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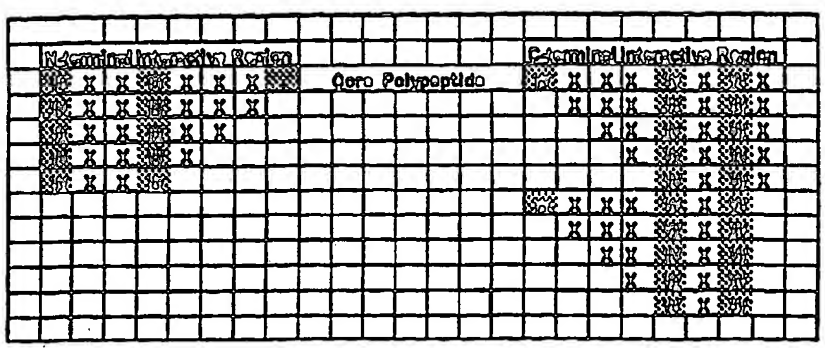

(57) Abstract

The present invention relates to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based on the discovery that hybrid polypeptides comprising the enhancer peptide sequences linked to a core polypeptide possess enhanced pharmacokinetic properties such as increased half life. The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide. The core polypeptides to be used in the practice of the invention can include any pharmacologically useful peptide that can be used, for example, as a therapeutic or prophylactic reagent.

HYBRID POLYPEPTIDES WITH ENHANCED PHARMACOKINETIC PROPERTIES

1. INTRODUCTION

The present invention relates to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based, in part, on the discovery that hybrid polypeptides comprising the enhancer peptide sequences linked to a core polypeptide possess enhanced pharmacokinetic properties such as increased half life. The invention further relates to novel anti-fusogenic and/or anti-viral, peptides, including ones that contain such enhancer peptide sequences, and methods for using such peptides. The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide. The core polypeptides to be used in the practice of the invention can include any pharmacologically useful peptide that can be used, for example, as a therapeutic or prophylactic reagent. In a non-limiting embodiment, the invention is demonstrated by way of example wherein a hybrid polypeptide comprising, for example, an HIV core polypeptide linked to enhancer peptide sequences, is shown to be a potent, non-cytotoxic inhibitor of HIV-1, HIV-2 and SIV infection. Additionally, the enhancer peptide sequences of the invention have been linked to a respiratory

syncytial virus (RSV) core polypeptide and a luteinizing hormone receptor (LH-RH) core polypeptide. In each instance, the hybrid polypeptide was found to possess enhanced pharmacokinetic properties, and the RSV hybrid polypeptide exhibited substantial anti-RSV activity.

2. BACKGROUND OF THE INVENTION

Polypeptide products have a wide range of uses as therapeutic and/or prophylactic reagents for prevention and treatment of disease. Many polypeptides are able to regulate biochemical or physiological processes to either prevent disease or provide relief from symptoms associated with disease. For example, polypeptides such as viral or bacterial polypeptides have been utilized successfully as vaccines for prevention of pathological diseases. Additionally, peptides have been successfully utilized as therapeutic agents for treatment of disease symptoms. Such peptides fall into diverse categories such, for example, as hormones, enzymes, immunomodulators, serum proteins and cytokines.

For polypeptides to manifest their proper biological and therapeutic effect on the target sites, the polypeptides must be present in appropriate concentrations at the sites of action. In addition, their structural integrity must generally be maintained. Therefore, the formulation of polypeptides as drugs for therapeutic use is directed by the chemical nature and the characteristics of the polypeptides, such as their size and complexity, their conformational requirements, and their often complicated stability, and solubility profiles. The pharmacokinetics of any particular therapeutic peptide is dependent on the bioavailability, distribution and clearance of said peptide.

Since many bioactive substances, such as peptides and proteins, are rapidly destroyed by the body, it is critical to develop effective systems for maintaining a steady concentration of peptide in blood circulation, to increase

the efficacy of such peptides, and to minimize the incidence and severity of adverse side effects.

3. SUMMARY OF THE INVENTION

The present invention relates, first, to enhancer peptide sequences originally derived from various retroviral envelope (gp41) protein sequences i.e., HIV-1, HIV-2 and SIV, that enhance the pharmacokinetic properties of any core polypeptide to which they are linked. The invention is based on the surprising result that when the disclosed enhancer peptide sequences are linked to any core polypeptide, the resulting hybrid polypeptide possesses enhanced pharmacokinetic properties including, for example, increased half life and reduced clearance rate relative to the core polypeptide alone. The present invention further relates to such hybrid polypeptides and core polypeptides, and to novel peptides that exhibit anti-fusogenic activity, antiviral activity and/or the ability to modulate intracellular processes that involve coiled-coil peptide structures. Among such peptides are ones that contain enhancer peptide sequences.

Core polypeptides can comprise any peptides which may be introduced into a living system, for example, any peptides capable of functioning as therapeutic, prophylactic or imaging reagents useful for treatment or prevention of disease or for diagnostic or prognostic methods, including methods in vivo imaging. Such peptides include, for example, growth factors, hormones, cytokines, angiogenic growth factors, extracellular matrix polypeptides, receptor ligands, agonists, antagonists or inverse agonists, peptide targeting agents, such as imaging agents or cytotoxic targeting agents, or polypeptides that exhibit antifusogenic and/or antiviral activity, and peptides or polypeptides that function as antigens or immunogens including, for example, viral and bacterial polypeptides.

The invention further relates to methods for enhancing the pharmacokinetic properties of any core polypeptide

through linkage of the core polypeptide to the enhancer peptide sequences to form hybrid polypeptides.

The invention still further relates to methods for using the peptides disclosed herein, including hybrid polypeptides containing enhancer peptide sequences. For example, the methods of the invention include methods for decreasing or inhibiting viral infection, e.g., HIV-1, HIV-2, RSV, measles, influenza, parainfluenza, Epstein-Barr, and hepatitis virus infection, and/or viral-induced cell fusion events. The enhancer peptide sequences of the invention can, additionally, be utilized to increase the in vitro or ex-vivo half-life of a core polypeptide to which enhancer peptide sequences have been attached, for example, enhancer peptide sequences can increase the half life of attached core polypeptides in cell culture or cell or tissue samples.

The invention is demonstrated by way of examples wherein hybrid polypeptides containing an HIV core polypeptide linked to enhancer peptide sequences are shown to exhibit greatly enhanced pharmacokinetic properties and act as a potent, non-cytotoxic inhibitors of HIV-1, HIV-2 and SIV infection. The invention is further demonstrated by examples wherein hybrid polypeptides containing an RSV core polypeptide or a luteinizing hormone polypeptide are shown to exhibit greatly enhanced pharmacokinetic properties. In addition, the RSV hybrid polypeptide exhibited substantial anti-RSV activity.

3.1. DEFINITIONS

Peptides, polypeptides and proteins are defined herein as organic compounds comprising two or more amino acids covalently joined, e.g., by peptide amide linages. Peptides, polypeptide and proteins may also include non-natural amino acids and any of the modifications and additional amino and carboxyl groups as are described herein. The terms "peptide," "polypeptide" and "protein" are, therefore, utilized interchangeably herein.

Peptide sequences defined herein are represented by one-letter symbols for amino acid residues as follows:

A (alanine)
R (arginine)
N (asparagine)
D (aspartic acid)
C (cysteine)
Q (glutamine)
E (glutamic acid)
G (glycine)
H (histidine)
I (isoleucine)
L (leucine)
K (lysine)
M (methionine)
F (phenylalanine)
P (proline)
S (serine)
T (threonine)
W (tryptophan)
Y (tyrosine)
V (valine)
X (any amino acid)

"Enhancer peptide sequences" are defined as peptides having the following consensus amino acid sequences: "WXXWXXXI", "WXXWXXX", "WXXWXX", "WXXWX", "WXXW", "WXXXWXWX", "XXXWXWX", "XXWXWX", "XWXWX", "WXWX", "WXXXWXW", "WXXXWX", "WXXXW", "IXXXWXXW", "XXXWXXW", "XXWXXW", "XWXXW", "XWXWXXXW", "XWXWXXX", "XWXWXX", "XWXWX", "XWXW", "WXWXXXW", or "XWXXXW", wherein X can be any amino acid, W represents tryptophan and I represents isoleucine. As discussed below, the enhancer peptide sequences of the invention also include peptide sequences that are otherwise the same as the consensus amino acid sequences but contain amino acid substitutions, insertions or deletions but which do not abolish the ability of the peptide to enhance the pharmacokinetic properties of a core peptide to which it is linked relative to the pharmacokinetic properties of the core polypeptide alone.

"Core polypeptide" as used herein, refers to any polypeptide which may be introduced into a living system and, thus, represents a bioactive molecule, for example any polypeptide that can function as a pharmacologically useful peptide for treatment or prevention of disease.

"Hybrid polypeptide" as used herein, refers to any polypeptide comprising an amino, carboxy, or amino and carboxy terminal enhancer peptide sequence and a core polypeptide. Typically, an enhancer peptide sequence is linked directly to a core polypeptide. It is to be understood that an enhancer peptide can also be attached to an intervening amino acid sequence present between the enhancer peptide sequence and the core peptide.

"Antifusogenic" and "anti-membrane fusion," as used herein, refer to a peptide's ability to inhibit or reduce the level of fusion events between two or more structures e.g., cell membranes or viral envelopes or pili, relative to the level of membrane fusion which occurs between the structures in the absence of the peptide.

"Antiviral," as used herein, refers to the peptide's ability to inhibit viral infection of cells via, e.g., cell fusion or free virus infection. Such infection can involve membrane fusion, as occurs in the case of enveloped viruses, or another fusion event involving a viral structure and a cellular structure, e.g., fusion of a viral pilus and bacterial membrane during bacterial conjugation).

4. BRIEF DESCRIPTION OF DRAWINGS

FIG. 1. Hybrid polypeptides. Enhancer peptide sequences derived from putative N-terminal and C-terminal interactive regions are depicted linked to a generic core polypeptide. Conserved enhancer peptide sequences are shaded. It is to be noted that the enhancer peptide sequences indicated may be used either as - terminal, C-terminal, or - and C-terminal additions. Further, the enhancer peptide sequences can be added to a core polypeptide in forward or reverse orientation, individually or in any of the possible combinations, to enhance pharmacokinetic properties of the peptide.

FIG. 2A. Enhancer peptide sequences derived from various envelope (gp41) protein sequences, representing the

N-terminal interactive region observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV. The final sequence "WXXWXXXI" represents a consensus sequence.

FIG. 2B. Enhancer peptide sequence variants derived from various envelope (gp41) protein sequences, representing the C-terminal interactive region observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV. The final sequence "WXXXWXWX" represents a consensus sequence.

FIG. 3. Comparison of HIV-1 titres in tissues of HIV-1 9320 infected SCID-HuPBMC mice as measured by P24 Levels in HuPBMC co-culture assays. The figure shows a comparison of in vivo T20 and T1249 viral inhibition.

FIG. 4A-4B. Plasma pharmacokinetic profile of T1249 vs. T1387 core control in CD-rats following IV injection for up to 2 hrs (FIG. 4A) and 8 hrs (FIG. 4B). The T1387 polypeptide is a core polypeptide and the T1249 polypeptide is the core polypeptide linked to enhancer peptide sequences.

FIG. 5. Plasma pharmacokinetic profile of T1249 vs. T20 control in CD-rats following IV administration. The T1249 polypeptide is a hybrid polypeptide of a core polypeptide (T1387) linked to enhancer peptide sequences. T20: n=4; T1249: n=3.

FIG. 6. Comparison of T20/T1249 Anti-HIV-1/IIIb activity and cytotoxicity.

FIG. 7. Direct Binding of T1249 to gp41 construct M41Δ178. ^{125}I-T1249 was HPLC purified to maximum specific activity. Saturation binding to M41Δ178 (a gp41 ectodomain fusion protein lacking the T20 amino acid sequence) immobilized in microtitre plates at 0.5 mg/ml is shown.

FIG. 8. Time Course of T1249 Association/Dissociation. The results demonstrate that ^{125}I-T1249 and ^{125}I-T20 have similar binding affinities of 1-2 nM. Initial on and off rates for ^{125}I-T1249 were significantly slower than those of 125I-T20. Dissociation of bound radioligand was measured following the addition of unlabeled peptide to a final concentration of 10μm in 1/10 total assay volume.

FIG. 9. Competition for T1249 Binding to M41Δ178. Unlabeled T1249 and T20 were titrated in the presence of a single concentration of either ^{125}I-T1249 or ^{125}I-T20. Ligand was added just after the unlabeled peptide to start the incubation.

FIG. 10A-10B. Plasma pharmacokinetic profile of RSV hybrid polypeptides T1301 (10A) and T1302 (10B) vs. T786 in CD rats.

FIG. 11A. Plaque Reduction Assay. Hybrid polypeptide T1293 is capable of inhibiting RSV infection with an IC_{50} 2.6 μg/ml.

FIG. 11B. Plaque Reduction Assay demonstrates the ability of RSV Hybrid Polypeptides T1301, T1302 and T1303 to inhibit RSV infection.

FIG. 12A and 12B. Plasma pharmacokinetic profile of luteinizing hormone hybrid polypeptide T1324 vs T1323 in CD male rats. The T1323 polypeptide is a luteinizing hormone core polypeptide and the T1324 polypeptide is a hybrid polypeptide comprising a core polypeptide linked to enhancer peptide sequences.

FIG. 13. Hybrid polypeptide sequences derived from various core polypeptides. Core polypeptide sequences are shown shaded. The non-shaded amino and carboxy terminal sequences represent enhancer peptide sequences.

FIG. 14A-B. Circular Dichroism (CD) spectra for T1249 in solution (phosphate buffered saline, pH 7) alone (10 μM at 1ºC; FIG. 14A) and in combination with a 45-residue peptide from the gp41 HR1 binding domain (T1346); the closed square (■) represents a theoretical CD spectrum predicted for a "non-interaction model" whereas the actual CD spectra are represented by the closed circle (•).

FIG. 15. Polyacrylamide gel electrophoresis showing T1249 protection of the gp41 construct M41Δ178 from proteinase-K digestion; lane 1: primer marker; lane 2: untreated M41Δ178; lane 3: M41Δ178 incubated with proteinase-K; lane 4: untreated T1249; lane 5: T1249 incubated with proteinase-K; lane 6: M41Δ178 incubated with T1249; lane 7: incubation of T1249 and M41Δ178 prior to addition of proteinase-K.

FIG. 16A-C. Pharmacokinetics of T1249 in Sprague-Dawley albino rats; FIG. 16A: pharmacokinetics of T1249 in a single dose administration by continuous subcutaneous infusion; FIG. 16B: Plasma pharmacokinetics of T1249 administered by subcutaneous injection (SC) or intravenous injection IV); FIG. 16C: Kinetic analysis of T1249 in lymph and plasma after intravenous administration.

FIG. 17A-B Pharmacokinetics of T1249 in cynomolgus monkeys; FIG. 17A: plasma pharmacokinetics of a single 0.8 mg/kg dose of T1249 via subcutaneous (SC) intravenous (IV) or intramuscular (IM) injection; FIG. 17B: Plasma pharmacokinetics of subcutaneously administered T1249 at three different dose levels (0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg).

5. DETAILED DESCRIPTION OF THE INVENTION

Described herein are peptide sequences, referred to as enhancer peptide sequences, derived from various retroviral

envelope (gp41) protein sequences that are capable of enhancing the pharmacokinetic properties of core polypeptides to which they are linked. Such enhancer peptide sequences can be utilized in methods for enhancing the pharmacokinetic properties of any core polypeptide through linkage of the enhancer peptide sequences to the core polypeptide to form a hybrid polypeptide with enhanced pharmacokinetic properties relative to the core polypeptide alone. The half life of a core peptide to which an enhancer peptide sequence or sequences has been attached can also be increased in vitro. For example, attached enhancer peptide sequences can increase the half life of a core polypeptide when present in cell culture, tissue culture or patient samples, such as cell, tissue, or other samples.

The core polypeptides of the hybrid polypeptides of the invention comprise any peptide which may be introduced into a living system, for example, any peptide that can function as a therapeutic or prophylactic reagent useful for treatment or prevention of disease, or an imaging agent useful for imaging structures in vivo.

Also described herein are peptides, including peptides that contain enhancer peptide sequences, that exhibit anti-fusogenic and/or anti-viral activity. Further described herein are methods for utilizing such peptides, including methods for decreasing or inhibiting viral infection and/or viral induced cell fusion.

5.1. HYBRID POLYPEPTIDES

The hybrid polypeptides of the invention comprise at least one enhancer peptide sequence and a core polypeptide. Preferably, the hybrid polypeptides of the invention comprise at least two enhancer peptide sequences and a core polypeptide, with at least one enhancer peptide present in the hybrid polypeptide amino to the core polypeptide and at least one enhancer peptide sequence present in the hybrid polypeptide carboxy to the core polypeptide.

The enhancer peptide sequences of the invention comprise peptide sequences originally derived from various retroviral envelope (gp 41) protein sequences, including HIV-1, HIV-2 and SIV sequences, and specific variations or modifications thereof described below. A core polypeptide can comprise any peptide sequence, preferably any peptide sequence that may be introduced into a living system, including, for example, peptides to be utilized for therapeutic, prophylactic or imaging purposes.

Typically, a hybrid polypeptide will range in length from about 10 to about 500 amino acid residues, with about 10 to about 100 amino acid residues in length being preferred, and about 10 to about 40 amino acids in length being most preferred.

While not wishing to be bound by any particular theory, the structure of the envelope protein is such that the putative α-helix region located in the C-terminal region of the protein is believed to associate with the leucine zipper region located in the N-terminal region of the protein. Alignment of the N-terminal and C-terminal enhancer peptide sequence gp41 regions observed in all currently published isolate sequences of HIV-1, HIV-2 and SIV identified consensus amino acid sequences.

In particular, the following consensus amino acid sequences representing consensus enhancer peptide sequences were identified (the consensus sequences are listed below in forward and reverse orientations because said enhancer peptide sequences can be utilized either in forward or reverse orientation): "WXXWXXXI", "WXXWXXX", "WXXWXX", "WXXWX", "WXXW", "WXXXWXWX", "XXXWXWX", "XXWXWX", "XWXWX", "WXWX", "WXXXWXW", "WXXXWX", "WXXXW", "IXXXWXXW", "XXXWXXW", "XXWXXW", "XWXXW", "XWXWXXXW", "XWXWXXX", "XWXWXX", "XWXWX", "XWXW", "WXWXXXW", or "XWXXXW", wherein X can be any amino acid, W represents tryptophan and I represents isoleucine. Forward orientations of consensus amino acid sequences are shown in FIGS. 1 and 2.

Typically, an enhancer peptide sequence will be about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 amino acid residues in length, with about 4 to about 20 residues in length being preferred, about 4 to about 10 residues in length being more preferred, and about 6 to about 8 residues in length being most preferred.

In a preferred embodiment of the invention, enhancer peptide sequences which may be used to enhance the pharmacokinetic properties of the resultant hybrid polypeptides comprise the specific enhancer peptide sequences depicted in FIGS. 2, 13, and Table 1, below. Among the most preferred enhancer peptide sequences are ones comprising the following amino sequence: "WQEWEQKI" and "WASLWEWF".

By way of example and not by way of limitation, Table 1, below, lists amino acid sequences that represent preferred embodiments of the enhancer peptide sequences of the enhancer peptide sequences of the invention. It is to be understood that while the forward orientation of these sequences is depicted below, the reverse orientation of the sequences is also intended to fall within the scope of the present invention. For example, while the forward orientation of the enhancer peptide sequence "WMEWDREI" is depicted below, its reverse orientation, <u>i.e.</u>, "IERDWEMW" is also intended to be included.

TABLE 1

WMEWDREI
WQEWERKV
WQEWEQKV
MTWMEWDREI
NNMTWMEWDREI
WQEWEQKVRYLEANI
NNMTWQEWEZKVRYLEANI
WNWFI

WQEWDREISNYTSLI
WQEWEREISAYTSLI
WQEWDREI
WQEWEI
WNWF
WQEW
WQAW
WQEWEQKI
WASLWNWF
WASLFNFF
WDVFTNWL
WASLWEWF
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AEWASLWAW
WAGLWAW
AEWAGLWAW
DKWEWF
IEWASLWEWF
IKWASLWEWF
DEWEWF
GGWASLWNWF
GGWNWF

In another preferred embodiment, particular enhancer peptide sequences of the invention comprise the enhancer peptide sequences depicted in FIGS. 2, 13 and Table 1 exhibiting conservative amino acid substitutions at one, two or three positions, wherein said substitutions do not abolish the ability of the enhancer peptide sequence to enhance the pharmacokinetic properties of a hybrid polypeptide relative to its corresponding core polypeptide.

Most preferably, such substitutions result in enhancer peptide sequences that fall within one of the enhancer peptide sequence consensus sequences. As such, generally, the substitutions are made at amino acid residues corresponding to the "X" positions depicted in the consensus amino acid sequences depicted above and in FIGS. 1 and 2. "Conservative substitutions" refer to substitutions with amino acid residues of similar charge, size and/or hydrophobicity/hydrophilicity characteristics as the amino acid residue being substituted. Such amino acid characteristics are well known to those of skill in the art.

The present invention further provides enhancer peptide sequences comprising amino acid sequences of FIGS. 1, 2, 13 and Table 1 that are otherwise the same, but, that said enhancer peptide sequences comprise one or more amino acid additions (generally no greater than about 15 amino acid residues in length), deletions (for example, amino- or terminal- truncations) or non-conservative substitutions which nevertheless do not abolish the resulting enhancer peptide's ability to increase the pharmacokinetic properties of core polypeptides to which they are linked relative to core polypeptides without such enhancer peptide sequences.

Additions are generally no greater than about 15 amino acid residues and can include additions of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 consecutive amino acid residues. Preferably the total number of amino acid residues added to the original enhancer peptide is no greater than about 15 amino acid residues, more preferably no greater

than about ten amino acid residues and most preferably no greater than about 5 amino acid residues.

Deletions are preferably deletions of no greater than about 3 amino acid residues in total (either consecutive or non-consecutive residues), more deletions preferably of 2 amino acids, most preferably deletions of single amino acids residues. Generally, deletions will be of amino acid residues corresponding to the "X" residues of the enhancer peptide consensus sequences.

Enhancer peptide sequences of the invention also comprise the particular enhancer peptide sequences depicted in FIGS. 2, 13 and Table 1 exhibiting one, two or three non-conservative amino acid substitutions, with two such substitutions being preferred and one such substitution being most preferred. "Non conservative" substitutions refer to substitutions with amino acid residues of dissimilar charge, size, and/or hydrophobicity/ hydrophilicity characteristics from the amino acid residue being replaced. Such amino acid characteristics are well known to those of skill in the art.

In addition, the amino acid substitutions need not be, and in certain embodiments preferably are not, restricted to the genetically encoded amino acids. Indeed, the peptides may contain genetically non-encoded amino acids. Thus, in addition to the naturally occurring genetically encoded amino acids, amino acid residues in the peptides may be substituted with naturally occurring non-encoded amino acids and synthetic amino acids.

Certain commonly encountered amino acids which provide useful substitutions include, but are not limited to, β-alanine (β-Ala) and other omega-amino acids such as 3-aminopropionic acid, 2,3-diaminopropionic acid (Dpr), 4-aminobutyric acid and so forth; α-aminoisobutyric acid (Aib); ε-aminohexanoic acid (Aha); δ-aminovaleric acid (Ava); N-methylglycine or sarcosine (MeGly); ornithine (Orn); citrulline (Cit); t-butylalanine (t-BuA); t-butylglycine (t-BuG); N-methylisoleucine (MeIle); phenylglycine (Phg); cyclohexylalanine (Cha); norleucine (Nle); naphthylalanine

(Nal); 4-chlorophenylalanine (Phe(4-Cl)); 2-fluorophenylalanine (Phe(2-F)); 3-fluorophenylalanine (Phe(3-F)); 4-fluorophenylalanine (Phe(4-F)); penicillamine (Pen); 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic); β-2-thienylalanine (Thi); methionine sulfoxide (MSO); homoarginine (hArg); N-acetyl lysine (AcLys); 2,4-diaminobutyric acid (Dbu); 2,3-diaminobutyric acid (Dab); *p*-aminophenylalanine (Phe(*p*NH_2)); N-methyl valine (MeVal); homocysteine (hCys), homophenylalanine (hPhe) and homoserine (hSer); hydroxyproline (Hyp), homoproline (hPro), N-methylated amino acids and peptoids (N-substituted glycines).

While in most instances, the amino acids of the peptide will be substituted with L-enantiomeric amino acids, the substitutions are not limited to L-enantiomeric amino acids. Thus, also included in the definition of "mutated" or "altered" forms are those situations where an L-amino acid is replaced with an identical D-amino acid (e.g., L-Arg → D-Arg) or with a D-amino acid of the same category or subcategory (e.g., L-Arg → D-Lys), and vice versa.

It is to be understood that the present invention also contemplates peptide analogues wherein one or more amide linkage is optionally replaced with a linkage other than amide, preferably a substituted amide or an isostere of amide. Thus, while the amino acid residues within peptides are generally described in terms of amino acids, and preferred embodiments of the invention are exemplified by way of peptides, one having skill in the art will recognize that in embodiments having non-amide linkages, the term "amino acid" or "residue" as used herein refers to other bifunctional moieties bearing groups similar in structure to the side chains of the amino acids. In addition the amino acid residues may be blocked or unblocked.

Additionally, one or more amide linkages can be replaced with peptidomimetic or amide mimetic moieties which do not

significantly interfere with the structure or activity of the peptides. Suitable amide mimetic moieties are described, for example, in Olson et al., 1993, J. Med. Chem. 36:3049.

Enhancer peptide sequences can be used to enhance the pharmacokinetic properties of the core polypeptide as either N-terminal, C-terminal, or - and C-terminal additions. While it is preferable for the enhancer peptide sequences to be utilized in a pairwise fashion, that is, preferably hybrid polypeptides comprise an enhancer peptide sequence at both the amino- and carboxy-termini, hybrid polypeptides can also comprise a single enhancer peptide, said peptide present at either the amino- or carboxy- terminus of the hybrid polypeptide. Further, the enhancer peptides can be used in either forward or reverse orientation, or in any possible combination, linked to a core polypeptide. It is noted that any of the enhancer peptides can be introduced at either the N-terminus or the C-terminus of the core polypeptide. Still further, multiple enhancer peptide sequences can be introduced to the N-, C-, or - and C-terminal positions of the hybrid polypeptides. Multiple enhancer peptide sequences can be linked directly one to another via the same sorts of linkages as used to link an enhancer peptide sequence to the core polypeptide (see below). In addition, an intervening amino acid sequence of the same sort as described below can also be present between one or more of the multiple enhancer peptide sequences. Multiple enhancer peptide sequences will typically contain from 2 to about 10 individual enhancer peptide sequences (of the same or different amino acid sequence), with about 2 to about 4 being preferred.

It is understood that the core polypeptide is generally linked to the enhancer peptides via a peptide amide linkage, although linkages other than amide linkages can be utilized to join the enhancer peptide sequences to the core polypeptides. Such linkages are well known to those of skill in the art and include, for example, any carbon-carbon, ester or chemical bond that functions to link the enhancer peptide sequences of the invention to a core peptide.

Typically, an enhancer peptide sequence is linked directly to a core polypeptide. An enhancer peptide sequence can also be attached to an intervening amino acid sequence present between the enhancer peptide sequence and the core polypeptide. The intervening amino acid sequence can typically range in size from about 1 to about 50 amino acid residues in length, with about 1 to about 10 residues in length being preferred. The same sorts of linkages described for linking the enhancer peptide to the core polypeptide can be used to link the enhancer peptide to the intervening peptide.

As discussed for enhancer peptide sequences, above, core and intervening amino acid sequences need not be restricted to the genetically encoded amino acids, but can comprise any of the amino acid and linkage modifications described above.

The amino- and/or carboxy-termini of the resulting hybrid polypeptide can comprise an amino group ($-NH_2$) or a carboxy (-COOH) group, respectively. Alternatively, the hybrid polypeptide amino-terminus may, for example, represent a hydrophobic group, including but not limited to carbobenzyl, dansyl, t-butoxycarbonyl, decanoyl, napthoyl or other carbohydrate group; an acetyl group; 9-fluorenylmethoxy-carbonyl (FMOC) group; or a modified, non-naturally occurring amino acid residue. Alternatively, the hybrid polypeptide carboxy-terminus can, for example, represent an amido group; a t-butoxycarbonyl group; or a modified non-naturally occurring amino acid residue. As a non-limiting example, the amino- and/or carboxy-termini of the resulting hybrid polypeptide can comprise any of the amino- and/or carboxy-terminal modifications depicted in the peptides shown in FIG. 13 or Table 2, below.

Typically, a hybrid polypeptide comprises an amino acid sequence that is a non-naturally occurring amino acid sequence. That is, typically, the amino acid sequence of a hybrid polypeptide, does not consist solely of the amino acid sequence of a fragment of an endogenous, naturally occurring polypeptide. In addition, a hybrid polypeptide is not

intended to consist solely of a full-length, naturally occurring polypeptide.

Core polypeptides can comprise any polypeptide which may be introduced into a living system, for example, any polypeptide that can function as a pharmacologically useful polypeptide. Such core polypeptides can, for example, be useful for the treatment or prevention of disease, or for use in diagnostic or prognostic methods, including in vivo imaging methods. The lower size limit of a core polypeptide is typically about 4-6 amino acid residues. There is, theoretically, no core polypeptide upper size limit and, as such a core polypeptide can comprise any naturally occurring polypeptide or fragment thereof, or any modified or synthetic polypeptide. Typically, however, a core polypeptide ranges from about 4-6 amino acids to about 494-500 amino acids, with about 4 to about 94-100 amino acid residues being preferred and about 4 to about 34-40 amino acid residues being most preferred.

Examples of possible core polypeptides, provided solely as example and not by way of limitation, include, but are not limited to, growth factors, cytokines, therapeutic polypeptides, hormones, e.g., insulin, and peptide fragments of hormones, inhibitors or enhancers of cytokines, peptide growth and differentiation factors, interleukins, chemokines, interferons, colony stimulating factors, angiogenic factors, receptor ligands, agonists, antagonists or inverse agonists, peptide targeting agents such as imaging agents or cytotoxic targeting agents, and extracellular matrix proteins such as collagen, laminin, fibronectin and integrin to name a few. In addition, possible core polypeptides may include viral or bacterial polypeptides that may function either directly or indirectly as immunogens or antigens, and thus may be useful in the treatment or prevention of pathological disease.

Representative examples of hybrid polypeptides which comprise core polypeptides derived from viral protein sequences are shown in FIG. 13, wherein the core polypeptide sequences are shaded. Core polypeptides also include, but

are not limited to, the polypeptides disclosed in U.S. Patent No. 5,464,933, U.S. Patent No. 5,656,480 and WO 96/19495, each of which is incorporated herein by reference in its entirety.

Core polypeptide sequences can further include, but are not limited to the polypeptide sequences depicted in Table 2, below. It is noted that the peptides listed in Table 2 include hybrid polypeptides in addition to core polypeptides. The sequence of the hybrid polypeptides will be apparent, however, in light of the terminal enhancer peptide sequences present as part of the hybrid polypeptides.

TABLE 2

T No.	Sequence
1	GIKQLQARILAVERYLKDQ
2	NNLLRAIEAQQHLLQLTVW
3	NEQELLELDKWASLWNWF
4	YTSLIHSLIEESQNQQEK
5	Ac-VWGIKQLQARILAVERYLKDQQLLGIWG-NH2
6	QHLLQLTVWGIKQLQARILAVERYLKDQ
7	LRAIEAQQHLLQLTVWGIKQLQARILAV
8	VQQQNNLLARIEAQQHLLQLTVWGIKQL
9	RQLLSGIVQQQNNLLRAIEAQQHLLQLT
10	MTLTVQARQLLSGIVQQQNNLLRAIEAQ
12	VVSLSNGVSVLTSKVLDLKNYIDKQLL
13	LLSTNKAVVSLSNGVSVLTSKVLDLKNY
15	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
19	Ac-LLSTNKAVVSLSNGVSVLTSKVLDLKNY-NH2
20	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
21	Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
22	Ac-IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-NH2
23	Ac-IELSNIKENKCNGTDAKVKLIKQELDKY-NH2
24	Ac-ENKCNGTDAKVKLIKQELDKYKNAVTEL-NH2
25	Ac-DAKVKLIKQELDKYKNAVTELQLLMQST-NH2
26	Ac-CNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
27	Ac-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
28	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
29	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
30	Ac-VLHLEGEVNKIKSALLSTHKAVVSLSNGVSVLTSK-NH2
31	Ac-ARKLQRMKQLEDKVEELLSKNYHYLENEVARLKKLV-NH2
32	Ac-RMKQLEDKVEELLSKNYHYLENEVARLKKLVGER-NH2
33	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQL-NH2
34	Ac-LRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
35	Ac-QHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
36	Ac-RQLLSGIVQQQNNLLRAIEAQQHLLQLT-NH2
37	Ac-MTLTVQARQLLSGIVQQQNNLLRAIEAQ-NH2
38	Ac-AKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
39	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
40	Ac-AKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVA-NH2
41	Ac-GTIALGVATSAQITAAVALVEAKQARSD-NH2
42	Ac-ATSAQITAAVALVEAKQARSDIEKLKEA-NH2
43	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKA-NH2
44	Ac-IEKLKEAIRDTNKAVQSVQSSIGNLIVA-NH2
45	Ac-IRDTNKAVQSVQSSIGNLIVAIKSVQDY-NH2
46	Ac-AVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
47	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLARILAVERYLKDQ-NH2
48	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQ-NH2
49	Ac-MTWMEWDREINNYTSLIGSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
50	Ac-WMEWDREINNYTSLIGSLIEESQNQQEKNEQELLE-NH2
51	Ac-INNYTSLIGSLIEESQNQQEKNEQELLE-NH2
52	Ac-INNYTSLIGSLIEESQNQQEKNEQELLELDKWASL-NH2
53	Ac-EWDREINNYTSLIGSLIEESQNQQEKNEQEGGC-NH2
54	Ac-QSRTLLAGIVQQQQQLLDVVKRQQELLR-NH2
55	Ac-NNDTWQEWERKVDFLEENITALLEEAQIQQEKNMYELQKLNSWD-NH2

T No.	Sequence
56	Ac-WQEWERKVDFLEENITALLEEAQIQQEK-NH2
57	Ac-VDFLEENITALLEEAQIQQEKNMYELQK-NH2
58	Ac-ITALLEEAQIQQEKNMYELQKLNSWDVF-NH2
59	Ac-SSESFTLLEQWNNWKLQLAEQWLEQINEKHYLEDIS-NH2
60	Ac-DKWASLWNWF-NH2
61	Ac-NEQELLELDKWASLWNWF-NH2
62	Ac-EKNEQELLELDKWASLWNWF-NH2
63	Ac-NQQEKNEQELLELDKWASLWNWF-NH2
64	Ac-ESQNQQEKNEQELLELDKWASLWNWF-NH2
65	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
66	Ac-NDQKKLMSNNVQIVRQQSYSIMSIIKEE-NH2
67	Ac-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
68	Ac-VSKGYSALRTGWYTSVITIELSNIKEN-NH2
69	Ac-VVSLSNGVSVLTSKVLDLKNYIDKQLL-NH2
70	Ac-VNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
71	Ac-PIINFYDPLVFPSDEFDASISQVNEKINQSLAFIR-NH2
72	Ac-NLVYAQLQFTYDTLRGYINRALAQIAEA-NH2
73	Ac-LNQVDLTETLERYQQRLNTYALVSKDASYRS-NH2
74	Ac-ELLVLKKAQLNRHSYLKDSDFLDAALD-NH2
75	Ac-LAEAGEESVTEDTEREDTEEEREDEEE-NH2
76	Ac-ALLAEAGEESVTEDTEREDTEEEREDEEEENEART-NH2
77	Ac-ETERSVDLVAALLAEAGEESVTEDTEREDTEEERE-NH2
78	Ac-EESVTEDTEREDTEEEREDEEEENEART-NH2
79	Ac-VDLVAALLAEAGEESVTEDTEREDTEEE-NH2
80	Ac-NSETERSVDLVAALLAEAGEESVTE-NH2
81	Ac-DISYAQLQFTYDVLKDYINDALRNIMDA-NH2
82	Ac-SNVFSKDEIMREYNSQKQHIRTLSAKVNDN-NH2
83	Biotin-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
84	Dig-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
85	Biotin-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
86	Dig-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
87	Ac-VLHQLNIQLKQYLETQERLLAGNRIAARQLLQIWKDVA-NH2
88	Ac-LWHEQLLNTAQRAGLQLQLINQALAVREKVLIRYDIQK-NH2
89	Ac-LLDNFESTWEQSKELWEQQEISIQNLHKSALQEYW-NH2
90	Ac-LSNLLQISNNSDEWLEALEIEHEKWKLTQWQSYEQF-NH2
91	Ac-KLEALEGKLEALEGKLEALEGKLEALEGKLEALEGK-NH2
92	Ac-ELRALRGELRALRGELRALRGELRALRGK-NH2
93	Ac-ELKAKELEGEGLAEGEEALKGLLEKAAKLEGLELLK-NH2
94	Ac-WEAAAREAAAREAAAREAAARA-NH2
95	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNAF-NH2
96	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANWF-NH2
97	Ac-YTSLIHSLIEESQNQQEKNQQELLELDKWASLWNWF-NH2
98	Ac-YTSLIHSLIEESQNQQEKNEQELLQLDKWASLWNWF-NH2
99	Ac-YTSLIHSLIEESQNQQEKNQQELLQLDKWASLWNWF-NH2
100	Ac-RMKQLEDKVEELLSKNYHLENEVARLKKLVGER-NH2
101	Ac-QQLLQLTVWGIKQLQARILAVERYLKNQ-NH2
102	Ac-NEQELLELDKWASLWNWF-NH2
103	Ac-YTSLIQSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
104	Ac-INFYDPLVFPSDEFDASISQVNEKINQSLAFIRK-NH2
105	Ac-INFYDPLVFPSDEFDASISQVNEKINQSLAFIRKS-NH2

T No.	Sequence
106	Ac-NFYDPLVFPSDEFDASISQVNEKINQSLAFIRKSD-NH2
107	Ac-FYDPLVFPSDEFDASISQVNEKINQSLAFIRKSDE-NH2
108	Ac-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
109	Ac-DPLVFPSDEFDASISQVNEKINQSLAFIRKSDELL-NH2
110	Ac-PLVFPSDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
111	Ac-LVFPSDEFDASISQVNEKINQSLAFIRKSDELLHN-NH2
112	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
113	Ac-FPSDEFDASISQVNEKINQSLAFIRKSDELLHNVN-NH2
114	Ac-PSDEFDASISQVNEKINQSLAFIRKSDELLHNVNA-NH2
115	Ac-SDEFDASISQVNEKINQSLAFIRKSDELLHNVNAG-NH2
116	Ac-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
117	Ac-EFDASISQVNEKINQSLAFIRKSDELLHNVNAGKS-NH2
118	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
119	Ac-DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTT-NH2
120	Ac-ASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSN-NH2
121	Ac-SGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNG-NH2
122	Ac-GVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGV-NH2
123	Ac-VAVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVS-NH2
124	Ac-AVSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSV-NH2
125	Ac-VSKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVL-NH2
126	Ac-SKVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLT-NH2
127	Ac-KVLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTS-NH2
128	Ac-VLHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSK-NH2
129	Ac-LHLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKV-NH2
130	Ac-HLEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVL-NH2
131	Ac-LEGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLD-NH2
132	Ac-EGEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDL-NH2
133	Ac-GEVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLK-NH2
134	Ac-EVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKN-NH2
135	Ac-VNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNY-NH2
136	Ac-NKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYI-NH2
137	Ac-KIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYID-NH2
138	Ac-IKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDK-NH2
139	Ac-KSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ-NH2
140	Ac-SALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQL-NH2
141	Ac-ALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLL-NH2
142	Ac-YTSVITIELSNIKENKCNGTDAKVKLIKQELDKYK-NH2
143	Ac-TSVITIELSNIKENKCNGTDAKVKLIKQELDKYKN-NH2
144	Ac-SVITIELSNIKENKCNGTDAKVKLIKQELDKYKNA-NH2
145	Ac-VITIELSNIKENKCNGTDAKVKLIKQELDKYKNAV-NH2
146	Ac-ITIELSNIKENKCNGTDAKVKLIKQELDKYKNAVT-NH2
147	Ac-TIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTE-NH2
148	Ac-IELSNIKENKCNGTDAKVKLIKQELDKYKNAVTEL-NH2
149	Ac-ELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQ-NH2
150	Ac-LSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQL-NH2
151	Ac-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
152	Ac-NIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLM-NH2
153	Ac-IKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQ-NH2
154	Ac-KENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQS-NH2
155	Ac-ENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQST-NH2

T No.	Sequence
156	Ac-LLDNFESTWEQSKELWELQEISIQNLHKSALQEYWN-NH2
157	Ac-ALGVATSAQITAAVALVEAKQARSDIEKLKEAIRD-NH2
158	Ac-LGVATSAQITAAVALVEAKQARSDIEKLKEAIRDT-NH2
159	Ac-GVATSAQITAAVALVEAKQARSDIEKLKEAIRDTN-NH2
160	Ac-VATSAQITAAVALVEAKQARSDIEKLKEAIRDTNK-NH2
161	Ac-ATSAQITAAVALVEAKQARSDIEKLKEAIRDTNKA-NH2
162	Ac-TSAQITAAVALVEAKQARSDIEKLKEAIRDTNKAV-NH2
163	Ac-SAQITAAVALVEAKQARSDIEKLKEAIRDTNKAVQ-NH2
164	Ac-AQITAAVALVEAKQARSDIEKLKEAIRDTNKAVQS-NH2
165	Ac-QITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSV-NH2
166	Ac-ITAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQ-NH2
167	Ac-TAAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQS-NH2
168	Ac-AAVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSS-NH2
169	Ac-AVALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSI-NH2
170	Ac-VALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIG-NH2
171	Ac-ALVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGN-NH2
172	Ac-LVEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNL-NH2
173	Ac-VEAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLI-NH2
174	Ac-EAKQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIV-NH2
175	Ac-KQARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAI-NH2
176	Ac-QARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIK-NH2
177	Ac-ARSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKS-NH2
178	Ac-RSDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSV-NH2
179	Ac-SDIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQ-NH2
180	Ac-DIEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQD-NH2
181	Ac-IEKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDY-NH2
182	Ac-EKLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYV-NH2
183	Ac-KLKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVN-NH2
184	Ac-LKEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNK-NH2
185	Ac-KEAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKE-NH2
186	Ac-EAIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEI-NH2
187	Ac-AIRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
188	Ac-IRDTNKAVQSVQSSIGNLIVAIKSVQDYVNKEIV-NH2
189	Ac-YTPNDITLNNSVALDPIDISIELNKAKSDLEESKE-NH2
190	Ac-TPNDITLNNSVALDPIDISIELNKAKSDLEESKEW-NH2
191	Ac-PNDITLNNSVALDPIDISIELNKAKSDLEESKEWI-NH2
192	Ac-NDITLNNSVALDPIDISIELNKAKSDLEESKEWIR-NH2
193	Ac-DITLNNSVALDPIDISIELNKAKSDLEESKEWIRR-NH2
194	Ac-ITLNNSVALDPIDISIELNKAKSDLEESKEWIRRS-NH2
195	Ac-TLNNSVALDPIDISIELNKAKSDLEESKEWIRRSN-NH2
196	Ac-LNNSVALDPIDISIELNKAKSDLEESKEWIRRSNQ-NH2
197	Ac-NNSVALDPIDISIELNKAKSDLEESKEWIRRSNQK-NH2
198	Ac-NSVALDPIDISIELNKAKSDLEESKEWIRRSNQKL-NH2
200	Ac-VALDPIDISIELNKAKSDLEESKEWIRRSNQKLDS-NH2
201	Ac-ALDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-NH2
202	Ac-LDPIDISIELNKAKSDLEESKEWIRRSNQKLDSIG-NH2
203	Ac-DPIDISIELNKAKSDLEESKEWIRRSNQKLDSIGN-NH2
204	Ac-PIDISIELNKAKSDLEESKEWIRRSNQKLDSIGNW-NH2
205	Ac-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-NH2
206	Ac-DISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQ-NH2

T No.	Sequence
207	Ac-ISIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQS-NH2
208	Ac-SIELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSS-NH2
209	Ac-IELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSST-NH2
210	Ac-ELNKAKSDLEESKEWIRRSNQKLDSIGNWHQSSTT-NH2
211	Ac-ELRALRGELRALRGELRALRGELRALRGELRALRGK-NH2
212	Ac-YTSLIHSLIEESQNQQQKNEQELLELDKWASLWNWF-NH2
213	Ac-YTSLIHSLIEESQNQQEKNEQELLELNKWASLWNWF-NH2
214	Ac-YTSLIHSLIEQSQNQQEKNEQELLELDKWASLWNWF-NH2
215	Ac-YTSLIHSLIQESQNQQEKNEQELLELDKWASLWNWF-NH2
216	Ac-YTSLIHSLIQQSQNQQQKNQQQLLQLNKWASLWNWF-NH2
217	Ac-EQELLELDKWASLWNWF-NH2
218	Ac-QELLELDKWASLWNWF-NH2
219	Ac-ELLELDKWASLWNWF-NH2
220	Ac-LLELDKWASLWNWF-NH2
221	Ac-LELDKWASLWNWF-NH2
222	Ac-ELDKWASLWNWF-NH2
226	Ac-WASLWNWF-NH2
227	Ac-ASLWNWF-NH2
229	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLANAA-NH2
230	Ac-YTSLIHSLIEESQNQQEKNEQQLLELDKWASLWNWF-NH2
231	Ac-YTSLIQSLIEESQNQQEKNQQELLELDKWASLWNWF-NH2
234	Ac-EAAAREAAAREAAARLELDKWASLWNWF-NH2
236	Ac-PSLRDPISAEISIQALSYALGGDINKVLEKLGYSG-NH2
237	Ac-SLRDPISAEISIQALSYALGGDINKVLEKLGYSGG-NH2
238	Ac-LRDPISAEISIQALSYALGGDINKVLEKLGYSGGD-NH2
239	Ac-RDPISAEISIQALSYALGGDINKVLEKLGYSGGDL-NH2
240	Ac-DPISAEISIQALSYALGGDINKVLEKLGYSGGDLL-NH2
241	Ac-PISAEISIQALSYALGGDINKVLEKLGYSGGDLLG-NH2
242	Ac-ISAEISIQALSYALGGDINKVLEKLGYSGGDLLGI-NH2
243	Ac-SAEISIQALSYALGGDINKVLEKLGYSGGDLLGIL-NH2
244	Ac-AEISIQALSYALGGDINKVLEKLGYSGGDLLGILE-NH2
245	Ac-EISIQALSYALGGDINKVLEKLGYSGGDLLGILES-NH2
246	Ac-ISIQALSYALGGDINKVLEKLGYSGGDLLGILESR-NH2
247	Ac-SIQALSYALGGDINKVLEKLGYSGGDLLGILESRG-NH2
248	Ac-IQALSYALGGDINKVLEKLGYSGGDLLGILESRGI-NH2
249	Ac-QALSYALGGDINKVLEKLGYSGGDLLGILESRGIK-NH2
250	Ac-ALSYALGGDINKVLEKLGYSGGDLLGILESRGIKA-NH2
251	Ac-LSYALGGDINKVLEKLGYSGGDLLGILESRGIKAR-NH2
252	Ac-PDAVYLHRIDLGPPISLERLDVGTNLGNAIAKLED-NH2
253	Ac-DAVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDA-NH2
254	Ac-AVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDAK-NH2
255	Ac-VYLHRIDLGPPISLERLDVGTNLGNAIAKLEDAKE-NH2
256	Ac-YLHRIDLGPPISLERLDVGTNLGNAIAKLEDAKEL-NH2
257	Ac-LHRIDLGPPISLERLDVGTNLGNAIAKLEDAKELL-NH2
258	Ac-HRIDLGPPISLERLDVGTNLGNAIAKLEDAKELLE-NH2
259	Ac-RIDLGPPISLERLDVGTNLGNAIAKLEDAKELLES-NH2
260	Ac-IDLGPPISLERLDVGTNLGNAIAKLEDAKELLESS-NH2
261	Ac-DLGPPISLERLDVGTNLGNAIAKLEDAKELLESSD-NH2
262	Ac-LGPPISLERLDVGTNLGNAIAKLEDAKELLESSDQ-NH2
263	Ac-GPPISLERLDVGTNLGNAIAKLEDAKELLESSDQI-NH2

T No.	Sequence
264	Ac-PPISLERLDVGTNLGNAIAKLEDAKELLESSDQIL-NH2
265	Ac-PISLERLDVGTNLGNAIAKLEDAKELLESSDQILR-NH2
266	Ac-ISLERLDVGTNLGNAIAKLEDAKELLESSDQILRS-NH2
267	Ac-SLERLDVGTNLGNAIAKLEDAKELLESSDQILRSM-NH2
268	Ac-LERLDVGTNLGNAIAKLEDAKELLESSDQILRSMK-NH2
269	Ac-EWIRRSNQKLDSI-NH2
270	Ac-LELDKWASLANAF-NH2
271	Ac-LELDKWASLFNFF-NH2
272	Ac-LELDKWASLANWF-NH2
273	Ac-LELDKWASLWNAF-NH2
274	Ac-ELGNVNNSISNALDKLEESNSKLDKVNVKLTSTSA-NH2
275	Ac-TELGNVNNSISNALDKLEESNSKLDKVNVKLTSTS-NH2
276	Ac-STELGNVNNSISNALDKLEESNSKLDKVNVKLTST-NH2
277	Ac-ISTELGNVNNSISNALDKLEESNSKLDKVNVKLTS-NH2
278	Ac-DISTELGNVNNSISNALDKLEESNSKLDKVNVKLT-NH2
279	Ac-LDISTELGNVNNSISNALDKLEESNSKLDKVNVKL-NH2
280	Ac-NLDISTELGNVNNSISNALDKLEESNSKLDKVNVK-NH2
281	Ac-GNLDISTELGNVNNSISNALDKLEESNSKLDKVNV-NH2
282	Ac-TGNLDISTELGNVNNSISNALDKLEESNSKLDKVN-NH2
283	Ac-VTGNLDISTELGNVNNSISNALDKLEESNSKLDKV-NH2
284	Ac-IVTGNLDISTELGNVNNSISNALDKLEESNSKLDK-NH2
285	Ac-VIVTGNLDISTELGNVNNSISNALDKLEESNSKLD-NH2
286	Ac-QVIVTGNLDISTELGNVNNSISNALDKLEESNSKL-NH2
287	Ac-SQVIVTGNLDISTELGNVNNSISNALDKLEESNSK-NH2
288	Ac-DSQVIVTGNLDISTELGNVNNSISNALDKLEESNS-NH2
289	Ac-LDSQVIVTGNLDISTELGNVNNSISNALDKLEESN-NH2
290	Ac-ILDSQVIVTGNLDISTELGNVNNSISNALDKLEES-NH2
291	Ac-SILDSQVIVTGNLDISTELGNVNNSISNALDKLEE-NH2
292	Ac-ISILDSQVIVTGNLDISTELGNVNNSISNALDKLE-NH2
293	Ac-NISILDSQVIVTGNLDISTELGNVNNSISNALDKL-NH2
294	Ac-KNISILDSQVIVTGNLDISTELGNVNNSISNALDK-NH2
295	Ac-QKNISILDSQVIVTGNLDISTELGNVNNSISNALD-NH2
296	Ac-YQKNISILDSQVIVTGNLDISTELGNVNNSISNAL-NH2
297	Ac-TYQKNISILDSQVIVTGNLDISTELGNVNNSISNA-NH2
298	Ac-ATYQKNISILDSQVIVTGNLDISTELGNVNNSISN-NH2
299	Ac-DATYQKNISILDSQVIVTGNLDISTELGNVNNSIS-NH2
300	Ac-FDATYQKNISILDSQVIVTGNLDISTELGNVNNSI-NH2
301	Ac-EFDATYQKNISILDSQVIVTGNLDISTELGNVNNS-NH2
302	Ac-GEFDATYQKNISILDSQVIVTGNLDISTELGNVNN-NH2
303	Ac-SGEFDATYQKNISILDSQVIVTGNLDISTELGNVN-NH2
304	Ac-LSGEFDATYQKNISILDSQVIVTGNLDISTELGNV-NH2
305	Ac-RLSGEFDATYQKNISILDSQVIVTGNLDISTELGN-NH2
306	Ac-LRLSGEFDATYQKNISILDSQVIVTGNLDISTELG-NH2
307	Ac-TLRLSGEFDATYQKNISILDSQVIVTGNLDISTEL-NH2
308	Ac-ITLRLSGEFDATYQKNISILDSQVIVTGNLDISTE-NH2
309	Ac-GITLRLSGEFDATYQKNISILDSQVIVTGNLDIST-NH2
310	Ac-TATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNNT-NH2
311	Ac-ITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFNN-NH2
312	Ac-SITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQFN-NH2
314	Ac-KESITATIEAVHEVTDGLSQLAVAVGKMQQFVNDQ-NH2

T No.	Sequence
315	Ac-LKESITATIEAVHEVTDGLSQLAVAVGKMQQFVND-NH2
316	Ac-RLKESITATIEAVHEVTDGLSQLAVAVGKMQQFVN-NH2
317	Ac-LRLKESITATIEAVHEVTDGLSQLAVAVGKMQQFV-NH2
318	Ac-ILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQF-NH2
319	Ac-NILRLKESITATIEAVHEVTDGLSQLAVAVGKMQQ-NH2
320	Ac-ANILRLKESITATIEAVHEVTDGLSQLAVAVGKMQ-NH2
321	Ac-AANILRLKESITATIEAVHEVTDGLSQLAVAVGKM-NH2
322	Ac-HKCDDECMNSVKNGTYDYPKYEEESKLNRNEIKGV-NH2
323	Ac-KCDDECMNSVKNGTYDYPKYEEESKLNRNEIKGVK-NH2
324	Ac-CDDECMNSVKNGTYDYPKYEEESKLNRNEIKGVKL-NH2
325	Ac-DDECMNSVKNGTYDYPKYEEESKLNRNEIKGVKLS-NH2
326	Ac-DECMNSVKNGTYDYPKYEEESKLNRNEIKGVKLSS-NH2
327	Ac-ECMNSVKNGTYDYPKYEEESKLNRNEIKGVKLSSM-NH2
328	Ac-CMNSVKNGTYDYPKYEEESKLNRNEIKGVKLSSMG-NH2
329	Ac-MNSVKNGTYDYPKYEEESKLNRNEIKGVKLSSMGV-NH2
330	Ac-NSVKNGTYDYPKYEEESKLNRNEIKGVKLSSMGVY-NH2
331	Ac-SVKNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQ-NH2
332	Ac-VKNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQI-NH2
333	Ac-KNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQIL-NH2
334	Ac-AFIRKSDELLHNV-NH2
335	Ac-VVLAGAALGVATAAQITAGIALHQSMLNSQAIDNL-NH2
336	Ac-VLAGAALGVATAAQITAGIALHQSMLNSQAIDNLR-NH2
337	Ac-LAGAALGVATAAQITAGIALHQSMLNSQAIDNLRA-NH2
338	Ac-AGAALGVATAAQITAGIALHQSMLNSQAIDNLRAS-NH2
339	Ac-GAALGVATAAQITAGIALHQSMLNSQAIDNLRASL-NH2
340	Ac-AALGVATAAQITAGIALHQSMLNSQAIDNLRASLE-NH2
341	Ac-ALGVATAAQITAGIALHQSMLNSQAIDNLRASLET-NH2
342	Ac-LGVATAAQITAGIALHQSMLNSQAIDNLRASLETT-NH2
343	Ac-GVATAAQITAGIALHQSMLNSQAIDNLRASLETTN-NH2
344	Ac-VATAAQITAGIALHQSMLNSQAIDNLRASLETTNQ-NH2
345	Ac-ATAAQITAGIALHQSMLNSQAIDNLRASLETTNQA-NH2
346	Ac-TAAQITAGIALHQSMLNSQAIDNLRASLETTNQAI-NH2
347	Ac-AAQITAGIALHQSMLNSQAIDNLRASLETTNQAIE-NH2
348	Ac-AQITAGIALHQSMLNSQAIDNLRASLETTNQAIEA-NH2
349	Ac-QITAGIALHQSMLNSQAIDNLRASLETTNQAIEAI-NH2
350	Ac-ITAGIALHQSMLNSQAIDNLRASLETTNQAIEAIR-NH2
351	Ac-TAGIALHQSMLNSQAIDNLRASLETTNQAIEAIRQ-NH2
352	Ac-AGIALHQSMLNSQAIDNLRASLETTNQAIEAIRQA-NH2
353	Ac-GIALHQSMLNSQAIDNLRASLETTNQAIEAIRQAG-NH2
354	Ac-IALHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQ-NH2
355	Ac-ALHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQE-NH2
356	Ac-LHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQEM-NH2
357	Ac-HQSMLNSQAIDNLRASLETTNQAIEAIRQAGQEMI-NH2
358	Ac-QSMLNSQAIDNLRASLETTNQAIEAIRQAGQEMIL-NH2
359	Ac-SMLNSQAIDNLRASLETTNQAIEAIRQAGQEMILA-NH2
360	Ac-MLNSQAIDNLRASLETTNQAIEAIRQAGQEMILAV-NH2
361	Ac-LNSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQ-NH2
362	Ac-NSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQG-NH2
363	Ac-SQAIDNLRASLETTNQAIEAIRQAGQEMILAVQGV-NH2
364	Ac-QAIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQ-NH2

T No.	Sequence
365	Ac-AIDHLRASLETTNQAIEAIRQAGQEMILAVQGVQD-NH2
366	Ac-IDHLRASLETTNQAIEAIRQAGQEMILAVQGVQDY-NH2
367	Ac-DHLRASLETTNQAIEAIRQAGQEMILAVQGVQDYI-NH2
368	Ac-NLRASLETTNQAIEAIRQAGQEMILAVQGVQDYIN-NH2
369	Ac-LRASLETTNQAIEAIRQAGQEMILAVQGVQDYINN-NH2
370	Ac-RASLETTNQAIEAIRQAGQEMILAVQGVQDYINNE-NH2
371	Ac-YTSVITIELSNIKENKCNGTDAVKLIKQELDKYK-NH2
372	Ac-TSVITIELSNIKENKCNGTDAVKLIKQELDKYKN-NH2
373	Ac-SVITIELSNIKENKCNGTDAVKLIKQELDKYKNA-NH2
374	Ac-SNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLL-NH2
375	Ac-KENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQS-NH2
376	Ac-CLELDKWASLWNWFC-NH2
377	Ac-CLELDKWASLANWFC-NH2
378	Ac-CLELDKWASLFNFFC-NH2
379	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLFNFF-NH2
381	Ac-RMKQLEDKVEELLSKNYHLENELELDKWASLWNWF-NH2
382	Ac-KVEELLSKNYHLENELELDKWASLWNWF-NH2
383	Ac-RMKQLEDKVEELLSKLEWIRRSNQKLDSI-NH2
384	Ac-RMKQLEDKVEELLSKLAFIRKSDELLHNV-NH2
385	Ac-ELEALRGELRALRGELELDKWASLWNWF-NH2
386	Ac-LDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-NH2
387	Ac-CNEQLSDSFPVEFFQV-NH2
388	Ac-MAEDDPYLGRPEQMFHLDPSL-NH2
389	Ac-EDFSSIADMDFSALLSQISS-NH2
390	Ac-TWQEWERKVDFLEENITALLEEAQIQQEKNMYELQ-NH2
391	Ac-WQEWERKVDFLEENITALLEEAQIQQEKNMYELQK-NH2
392	Ac-QEWERKVDFLEENITALLEEAQIQQEKNMYELQKL-NH2
393	Ac-EWERKVDFLEENITALLEEAQIQQEKNMYELQKLN-NH2
394	Ac-WERKVDFLEENITALLEEAQIQQEKNMYELQKLNS-NH2
395	Ac-ERKVDFLEENITALLEEAQIQQEKNMYELQKLNSW-NH2
396	Ac-RKVDFLEENITALLEEAQIQQEKNMYELQKLNSWD-NH2
397	Ac-KVDFLEENITALLEEAQIQQEKNMYELQKLNSWDV-NH2
398	Ac-VDFLEENITALLEEAQIQQEKNMYELQKLNSWDVF-NH2
399	Ac-DFLEENITALLEEAQIQQEKNMYELQKLNSWDVFG-NH2
400	Ac-FLEENITALLEEAQIQQEKNMYELQKLNSWDVFGN-NH2
401	Ac-LEENITALLEEAQIQQEKNMYELQKLNSWDVFGNW-NH2
402	Ac-LEENITALLEEAQIQQEKNMYELQKLNSWDVFGNWF-NH2
403	Ac-NEQSEEKENELYWAKEQLLDLLFNIFNQTVGAWIMQ-NH2
405	Ac-QQQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
406	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
407	Ac-QQLLDVVKRQQELLRLTVWGPKNLQTRVTAIEKYLKDQ-NH2
408	Ac-DERKQDKVLVVQQTGTLQLTLIQLEKTAKLQWVRLNRY-NH2
409	Ac-QQQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKY-NH2
410	Ac-QQLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYL-NH2
411	Ac-QLLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLK-NH2
412	Ac-LLDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKD-NH2
413	Ac-LDVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQ-NH2
414	Ac-DVVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQA-NH2
415	Ac-VVKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQ-NH2
416	Ac-VKRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQL-NH2

T. No.	Sequence
417	Ac-KRQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQLN-NH2
418	Ac-RQQELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNA-NH2
419	Ac-QQELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAW-NH2
420	Ac-QELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAWG-NH2
421	Ac-ELLRLTVWGTKNLQTRVTAIEKYLKDQAQLNAWGC-NH2
422	Ac-NNLLRAIEAQQHLLQLTVWGPKQLQARILAVERYLKDQ-NH2
423	Ac-SELEIKRYKNRVASRKCRAKFKQLLQHYREVAAAK-NH2
424	Ac-ELEIKRYKNRVASRKCRAKFKQLLQHYREVAAAKS-NH2
425	Ac-LEIKRYKNRVASRKCRAKFKQLLQHYREVAAAKSS-NH2
426	Ac-EIKRYKNRVASRKCRAKFKQLLQHYREVAAAKSSE-NH2
427	Ac-IKRYKNRVASRKCRAKFKQLLQHYREVAAAKSSEN-NH2
428	Ac-KRYKNRVASRKCRAKFKQLLQHYREVAAAKSSEND-NH2
429	Ac-RYKNRVASRKCRAKFKQLLQHYREVAAAKSSENDR-NH2
430	Ac-YKNRVASRKCRAKFKQLLQHYREVAAAKSSENDRL-NH2
431	Ac-KNRVASRKCRAKFKQLLQHYREVAAAKSSENDRLR-NH2
432	Ac-NRVASRKCRAKFKQLLQHYREVAAAKSSENDRLRL-NH2
433	Ac-RVASRKCRAKFKQLLQHYREVAAAKSSENDRLRLL-NH2
434	Ac-VASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLL-NH2
435	Ac-ASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLK-NH2
436	Ac-SRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQ-NH2
437	Ac-RKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQM-NH2
438	Ac-KCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMC-NH2
439	Ac-CRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-NH2
440	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPS-NH2
441	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSL-NH2
442	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLD-NH2
443	Ac-FKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDV-NH2
444	Ac-KQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVD-NH2
445	Ac-QLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
446	Ac-LLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSI-NH2
447	Ac-LQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSII-NH2
448	Ac-QHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIP-NH2
449	Ac-HYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPR-NH2
450	Ac-YREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRT-NH2
451	Ac-REVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTP-NH2
452	Ac-EVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
453	Ac-VAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDV-NH2
454	Ac-AAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVL-NH2
455	Ac-AAKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLH-NH2
456	Ac-AKSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHE-NH2
457	Ac-KSSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHED-NH2
458	Ac-SSENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDL-NH2
459	Ac-SENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLL-NH2
460	Ac-ENDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLLN-NH2
461	Ac-NDRLRLLLKQMCPSLDVDSIIPRTPDVLHEDLLNF-NH2
634	Ac-PGYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGML-NH2
635	Ac-GYRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLP-NH2
636	Ac-YRWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPV-NH2
637	Ac-RWMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVC-NH2
638	Ac-WMCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCP-NH2

T No.	Sequence
• 639	Ac-MCLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPL-NH2
• 640	Ac-CLRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLI-NH2
• 641	Ac-LRRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIP-NH2
• 642	Ac-RRFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPG-NH2
• 643	Ac-RFIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGS-NH2
• 644	Ac-FIIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSS-NH2
• 645	Ac-IIFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSST-NH2
• 646	Ac-IFLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTT-NH2
• 647	Ac-FLFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTS-NH2
• 648	Ac-LFILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTST-NH2
• 649	Ac-FILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTG-NH2
• 650	Ac-ILLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGP-NH2
• 651	Ac-LLLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPC-NH2
• 652	Ac-LLCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCR-NH2
• 653	Ac-LCLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRT-NH2
654	Ac-CLIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTC-NH2
655	Ac-LIFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCM-NH2
656	Ac-IFLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMT-NH2
657	Ac-FLLVLLDYQGMLPVCPLIPGSSTTSTGPCRTCMTT-NH2
658	Ac-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
659	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
660	Ac-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
661	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
662	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
663	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
664	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
665	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
666	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
667	Ac-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
668	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
669	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
670	Ac-FWNWLSAWKDLELKSLLEEVKDELQKMR-NH2
671	NNLLRAIEAQQHLLQLTVW-NH2
672	Ac-CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
673	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
674	C13H27CO-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
675	Ac-AVSKGYLSALRTGWYTSVITIELSNIKENKCNGTDA-NH2
676	Ac-SISNIETVIEFQQKNNRLLEITREFSVNAGVTTPVS-NH2
677	Ac-DQQSKQYKRLLDRLIIPLYDGLRQKDVIVSNQESN-NH2
678	Ac-YSELTNIFGDNIGSLQEKGIKLQGIASLYRTNITEI-NH2
679	Ac-TSITLQVRLPLLTRLLNTQIYRVDSISYNIQNREWY-NH2
680	Ac-VEIAEYRRLLRTVLEPIRDALNAMTQNIRPVQSVA-NH2
681	Ac-SYFIVLSIAYPTLSEIKGVIVHRLEGVSYNIGSQEW-NH2
682	Ac-LKEAIRDTNKAVQSVQSSIGNLIVAIKS-NH2
683	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
683	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
684	QKQEPIDKELYPLTSL
685	YPKFVKQNTLKLAT
686	QYIKANSKFIGITE
687	NGQIGNDPNRDILY

T. No.	Sequence
588	Ac-RPDVY-OH
589	CLELDKWASLWNWFC-(cyclic)
590	CLELDKWASLANWFC-(cyclic)
591	CLELDKWASLANFFC-(cyclic)
594	Ac-NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
595	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
596	Ac-PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
597	Ac-LLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTT-NH2
598	Ac-LVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTV-NH2
599	Ac-VLQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVC-NH2
600	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCL-NH2
601	Ac-QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLG-NH2
602	Ac-AGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQ-NH2
603	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQN-NH2
604	Ac-FFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNS-NH2
605	Ac-FLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQ-NH2
606	Ac-LLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQS-NH2
607	Ac-LTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQSP-NH2
608	Ac-LELDKWASLWNWA-NH2
609	Ac-LELDKWASAWNWF-NH2
610	Ac-LELDKAASLWNWF-NH2
611	Ac-LKLDKWASLWNWF-NH2
612	Ac-LELKKWASLWNWF-NH2
613	Ac-DELLHNVNAGKST-NH2
614	Ac-KSDELLHNVNAGKST-NH2
615	Ac-IRKSDELLHNVNAGKST-NH2
616	Ac-AFIRKSDELLHNVNAGKST-NH2
617	Ac-FDASISQVNEKINQSLAFI-NH2
618	Ac-YAADKESTQKAFDGITNKVNSVIEKMNTQFEAVGKE-NH2
619	Ac-SVIEKMNTQFEAVGKEFGNLERRLENLNKRMEDGFL-NH2
620	Ac-VWTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
621	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2
622	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
623	Ac-INNYTSLIHSLIEESQNQQEKNEQELLE-NH2
624	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
625	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
626	Ac-IDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
627	Ac-NQQEKNEQELLELDKWASLWNWFNITNWLWYIKIFI-NH2
627	Ac-NQQEKNEQELLELDKWASLWNWFNITNWLWYIKIFI-NH2
628	Ac-QNQQEKNEQELLELDKWASLWNWFNITNWLWYIKIF-NH2
629	Ac-SQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKI-NH2
630	Ac-ESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIK-NH2
631	Ac-EESQNQQEKNEQELLELDKWASLWNWFNITNWLWYI-NH2
632	Ac-IEESQNQQEKNEQELLELDKWASLWNWFNITNWLWY-NH2
633	Ac-LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLW-NH2
634	Ac-SLIEESQNQQEKNEQELLELDKWASLWNWFNITNWL-NH2
635	Ac-HSLIEESQNQQEKNEQELLELDKWASLWNWFNITNW-NH2
636	Ac-IHSLIEESQNQQEKNEQELLELDKWASLWNWFNITN-NH2
637	Ac-LIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-NH2
638	Ac-SLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2

T No.	Sequence
639	Ac-TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
640	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW-NH2
641	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
642	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW-NH2
643	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
644	Ac-REINNYTSLIHSLIEESQNQQEKNEQELLELDKWAS-NH2
645	Ac-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWA-NH2
646	Ac-WDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-NH2
647	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-NH2
648	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLELD-NH2
649	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
650	Ac-TWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
651	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
652	Ac-NMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
653	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
654	Ac-WNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQ-NH2
655	Ac-IWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNE-NH2
656	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKN-NH2
657	Ac-EQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEK-NH2
658	Ac-LEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQE-NH2
659	Ac-SLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQ-NH2
660	Ac-KSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQ-NH2
661	Ac-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQN-NH2
662	Ac-SLAFIRKSDELLHNVNAGKST-NH2
663	Ac-FDASISQVNEKINQSLAFIRK-NH2
664	Ac-YTSLIHSLIEESQQQQEKQEQELLELDKWASLWNWF-NH2
665	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
666	Ac-FDASISQVNEKINQSLAFIRKSDELLHNVNA-NH2
667	Ac-FDASISQVNEKINQSLAFIRKSDELLHNV-NH2
668	Ac-FDASISQVNEKINQSLAFIRKSDELLH-NH2
669	Ac-FDASISQVNEKINQSLAFIRKSDEL-NH2
670	Ac-FDASISQVNEKINQSLAFIRKSD-NH2
671	Ac-ASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
672	Ac-ISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
673	Ac-QVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
674	Ac-NEKINQSLAFIRKSDELLHNVNAGKST-NH2
675	Ac-KINQSLAFIRKSDELLHNVNAGKST-NH2
676	Ac-NQSLAFIRKSDELLHNVNAGKST-NH2
677	Ac-FWNWLSAWKDLELYPGSLELDKWASLWNWF-NH2
678	Ac-CGGNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
679	Ac-CGGYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
680	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
681	NNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ
682	Ac-EKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQYGV-NH2
683	Ac-QEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQYG-NH2
684	Ac-QQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQY-NH2
685	Ac-IQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYIQ-NH2
686	Ac-QIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQYI-NH2
687	Ac-AQIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQY-NH2
688	Ac-QAQIQQEKNMYELQKLNSWDVFTNWLDFTSWVRYIQ-NH2

T. No.	Sequence
741	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYL-NH2
742	Ac-VQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
743	Ac-IVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVER-NH2
744	Ac-GIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVE-NH2
745	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAV-NH2
758	Ac-RSMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTV-NH2
760	Ac-GARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
764	Ac-GSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQH-NH2
765	Ac-GSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQH-NH2
766	Ac-EGSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
767	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLL-NH2
768	Ac-AKFKQLLQHYREVAAAKSSENDRLRLLL-NH2
769	Ac-KFKQLLQHYREVAAAKSSENDRLRLLLK-NH2
770	Ac-FKQLLQHYREVAAAKSSENDRLRLLLKQ-NH2
771	Ac-RAKFKQELQHYREVAAAKSSENDRLRLLLKQMCPS-NH2
772	DKWASLWNWF-NH2
773	Biotin-FDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
774	Ac-YDASISQVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
775	Ac-YDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
776	Ac-FDASISQVNEKINQSLAYIRKSDELLHNVNAGKST-NH2
777	Ac-FDASISQVQEKIQQSLAFIRKSDELLHQVQAGKST-NH2
778	Ac-FDASISQVNEKINQALAFIRKADELLHNVNAGKST-NH2
779	Ac-FDASISQVNEKINQALAFIRKSDELLHNVNAGKST-NH2
780	Ac-FDASISQVNEKINQSLAFIRKADELLHNVNAGKST-NH2
781	Ac-YDASISQVQEEIQQALAFIRKADELLEQVQAGKST-NH2
782	Ac-FDASISQVNEKINQSLAFIRKSDELLENVNAGKST-NH2
783	Ac-FDASISQVNEEINQSLAFIRKSDELLHNVNAGKST-NH2
784	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLENV-NH2
785	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLENV-NH2
786	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
787	Ac-VFPSDEFDASISQVNEEINQSLAFIRKSDELLHNV-NH2
788	Ac-SNKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQ-NH2
789	Ac-WSNKSLEQIWNNMTWMEWDREINNYTSLIHSLIEES-NH2
790	Ac-SWSNKSLEQIWNNMTWMEWDREINNYTSLIHSLIEE-NH2
791	Ac-ASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSLIE-NH2
792	Ac-NASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSLI-NH2
793	Ac-WNASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSL-NH2
793	Ac-WNASWSNKSLEQIWNNMTWMEWDREINNYTSLIHSL-NH2
794	Ac-PWNASWSNKSLEQIWNNMTWMEWDREINNYTSLIHS-NH2
795	Ac-VPWNASWSNKSLEQIWNNMTWMEWDREINNYTSLIH-NH2
796	Ac-AVPWNASWSNKSLEQIWNNMTWMEWDREINNYTSLI-NH2
797	Ac-TAVPWNASWSNKSLEQIWNNMTWMEWDREINNYTSL-NH2
798	Ac-TTAVPWNASWSNKSLEQIWNNMTWMEWDREINNYTS-NH2
800	Ac-AAASDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
801	Ac-VFPAAAFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
802	Ac-VFPSDEAAASISQVNEKINQSLAFIRKSDELLHNV-NH2
803	Ac-VFPSDEFDAAAAQVNEKINQSLAFIRKSDELLHNV-NH2
804	Ac-VFPSDEFDASISAAAEKINQSLAFIRKSDELLHNV-NH2
805	Ac-VFPSDEFDASISQVNAAANQSLAFIRKSDELLHNV-NH2
806	Ac-VFPSDEFDASISQVNEKIAAALAFIRKSDELLHNV-NH2

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807	Ac-VFPSDEFDASISQVNEKINQSAAAIRKSDELLHNV-NH2
808	Ac-VFPSDEFDASISQVNEKINQSLAFAAASDELLHNV-NH2
809	Ac-VFPSDEFDASISQVNEKINQSLAFIRKAAALLHNV-NH2
810	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEAAANV-NH2
811	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLAAA-NH2
812	Ac-VYPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
813	Ac-AAAAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
814	Ac-YTSLIHSLIEESQQQQEKNEQELLELDKWASLWNWF-NH2
815	Ac-YTSLIHSLIEESQNQQEKQEQELLELDKWASLWNWF-NH2
816	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKQ-NH2
817	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQQQQEKN-NH2
818	Ac-QIWNNMTWMEWDREINNYTSLIHSLIEESQQQQEKQ-NH2
819	Ac-NKSLEQIWNNMTWMEWDREINNYTSLIHSLIEESQQ-NH2
820	Ac-FDASISQVNEKINQSLAFIEESDELLHNVNAGKST-NH2
821	Ac-ACIRKSDELCL-NH2
823	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2
824	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2
825	Ac-YTSLIHSLIEESQDQQEKDEQELLELDKWASLWNWF-NH2
826	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDWF-NH2
841	Ac-LEANITQSLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
842	Ac-LEANISASLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
843	Ac-LEANISALLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
844	Ac-LEANITALLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
845	Ac-LEANITASLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
845	Ac-LEANITASLEQAQIQQEKNMYELQKLNSWDVFTNWL-NH2
846	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMUPS-NH2
847	Ac-Abu-DDE-Abu-MNSVKNGTYDYPKYEEESKLNRNEIKGVKL-NH2
856	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNMYELQKL-NH2
860	Ac-DEYDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
861	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
862	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLW-NH2
863	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
864	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAS-NH2
865	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
866	Ac-DREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
867	Ac-NNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDK-NH2
868	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWAAA-NH2
869	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAAAANWF-NH2
870	Ac-YTSLIHSLIEESQNQQEKNEQELLELDAAASLWNWF-NH2
871	Ac-YTSLIHSLIEESQNQQEKNEQELLAAAKWASLWNWF-NH2
872	Ac-YTSLIHSLIEESQNQQEKNEQAAAELDKWASLWNWF-NH2
873	Ac-YTSLIHSLIEESQNQQEKAAAELLELDKWASLWNWF-NH2
874	Ac-YTSLIHSLIEESQNQAAANEQELLELDKWASLWNWF-NH2
875	Ac-YTSLIHSLIEESAAAQEKNEQELLELDKWASLWNWF-NH2
876	Ac-YTSLIHSLIAAAQNQQEKNEQELLELDKWASLWNWF-NH2
877	Ac-YTSLIHAAAEESQNQQEKNEQELLELDKWASLWNWF-NH2
878	Ac-YTSAAASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
879	Ac-EWNNMTWMEWDRENEKINQSLAFIRKSDELLHNV-NH2
880	Ac-YISEVNEEINQSLAFIRKADELLENVDKWASLWNWF-NH2
881	Ac-TSVITIELSNIKENKANGTDAKVKLIKQELDKYKN-NH2

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882	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFMG-NH2
883	Ac-NEKINQSLAFIRKSDELLHNV-NH2
884	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
885	Biotin-PLVFPSDEFDASISQVNEKINQSLAFIRKSDELLH-NH2
886	Biotin-VFPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
887	Biotin-DEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
888	Biotin-VYPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
889	Biotin-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
890	Ac-VYPSDEFDASISQVQEEIQQALAFIRKADELLEQV-NH2
891	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
892	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
893	Ac-INNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
894	Ac-EINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
895	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
896	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
897	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNIT-NH2
898	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITN-NH2
899	Ac-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDELLHNVNAGK-NH2
900	Ac-NYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFN-NH2
901	Ac-NNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNI-NH2
905	Ac-KCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
906	Ac-RAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDSIIPRTPD-NH2
907	Ac-VYPSDEYDASISQVNEEINQALAYIAAADELLENV-NH2
909	Ac-YDASISQVNEEINQALAYIRKADELL-NH2
910	Ac-M-Nle-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
911	Ac-KNGTYDYPKYEEESKLNRNEIKGVKLSSMGVYQI-NH2
912	Ac-VTEKIQMASDNINDLIQSGVNTRLLTIQSHVQNYI-NH2
913	QNQQEKNEQELLELDKWASLWNWF-NH2
914	Ac-QNQQEKNEQELLELDKWASLWNWF-NH2
915	LWNWF-NH2
916	ELLELDKWASLWNWF-NH2
917	EKNEQELLELDKWASLWNWF-NH2
918	SLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
919	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNW
920	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN
921	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLW
922	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASL
923	TSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
924	SLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
925	LIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
926	IHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
940	Ac-AAVALLPAVLLALLAPSELEIKRYKNRVASRKCRAKFKQLLQHYREVAAAK-NH2
941	Ac-AAVALLPAVLLALLAPCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCP-NH2
942	Ac-YTSLIHSLIEESQNQQEKNNNIERDWEMWTMNNWIQ-NH2
944	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
945	Ac-LMQLARQLMQLARQMKQLADSLMQLARQVSRLESA-NH2
946	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
947	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
948	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
949	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2

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950	Biotin-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
951	Ac-YLEYDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
952	Ac-IKQFINMWQEVGKAMYA-NH2
953	Ac-IRKSDELL-NH2
954	Decanoyl-IRKSDELL-NH2
955	Acetyl-Aca-Aca-IRKSDELL-NH2
956	Ac-YDASISQV-NH2
957	Ac-NEKINQSL-NH2
958	Ac-SISQVNEEINQALAYIRKADELL-NH2
959	Ac-QVNEEINQALAYIRKADELL-NH2
960	Ac-EEINQALAYIRKADELL-NH
961	Ac-NQALAYIRKADELL-NH2
962	Ac-LAYIRKADELL-NH2
963	FDASISQVNEKINQALAFIRKSDELL-NH2
964	Ac-W-Nle-EWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
965	Ac-ASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
967	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQELLEL-NH2
968	Ac-YVKGEPIINFYDPLVFPSDEFDASISQVNEKINQSL-NH2
969	Ac-VYPSDEYDASISQVNEEINQSLAYIRKADELLHNV-NH2
970	Ac-YDASISQVNEEINQALAYIRKADELLENV-NH2
971	Ac-YDASISQVNEEINQALAYIRKADELLE-NH2
972	Ac-VYPSDEYDASISQVNEEINQALAYIRKAAELLHNV-NH2
973	Ac-VYPSDEYDASISQVNEEINQALAYIRKALELLHNV-NH2
974	Decanoyl-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
975	Ac-VYPSDEYDASISQVNEEINQLLAYIRKLDELLENV-NH2
976	Ac-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
977	Ac-SNDQGSGYAADKESTQKAFDGITNKVNSVIEKTNT-NH2
978	Ac-ESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
979	Ac-DGITNKVNSVIEKTNTQFEAVGKEFGNLEKRLENLNK-NH2
980	Ac-DSNVKNLYDKVRSQLRDNVKELGNGAFEFYHK-NH2
981	Ac-RDNVKELGNGAFEFYHKADDEALNSVKNGTYDYPKY-NH2
982	Ac-EFYHKADDEALNSVKNGTYDYPKY-NH2
983	Ac-AAVALLPAVLLALLAPAADKESTQKAFDGITNKVNS-NH2
984	Ac-AAVALLPAVLLALLAPAADSNVKNLYDKVRSQLRDN-NH2
985	Ac-KESTQKAFDGITNKVNSV-NH2
986	Ac-IEKTNTQFEAVGKEFGNLER-NH2
987	Ac-RLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
988	Ac-SNVKNLYDKVRSQLRDN-NH2
989	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
990	Ac-WMEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
991	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
992	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQE-NH2
993	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELLE-NH2
994	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
995	Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
996	Ac-YTKFIYTLLEESQNQQEKNEQELLELDKWASLWNWF-NH2
997	Ac-YMKQLADSLMQLARQVSRLESA-NH2
998	Ac-YLMQLARQMKQLADSLMQLARQVSRLESA-NH2
999	Ac-YQEWERKVDFLEENITALLEEAQIQQEKNMYELQKL-NH2
1000	Ac-WMAWAAAAINNYTSLIHSLIEESQNQQEKNEQEEEEE-NH2

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1001	Ac-YASLIAALIEESQNQQEKNEQELLELAKWAALWAWF-NH2
1002	[Ac-EWDREINNYTSLIHSLIEESQNQQEKNEQEGGC-NH2]dimer
1003	Ac-YDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
1004	Biotinyl-HDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
1005	Ac-YTSLI-OH
1006	Fmoc-HSLIEE-OH
1007	Fmoc-SQNQQEK-OH
1008	Fmoc-NEQELLEL-OH
1009	Fmoc-DKWASL-OH
1010	Fmoc-WNWF-OH
1011	Ac-AKTLERTWDTLNHLLFISSALYKLNLKSVAQITLSI-NH2
1012	Ac-NITLQAKIKQFINMWQEVGKAMYA-NH2
1013	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDN-NH2
1014	Ac-LENERTLDFHDSNVKNLYDKVRLQLRDNVKELGNG-NH2
1015	Ac-TLDFHDSNVKNLYDKVRLQLRDNVKELGNGAFEF-NH2

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1016	Ac-IDISIELNKAKSDLEESKEWIKKSNQKLDSIGNWH-NH2
1021	Biotinyl-SISQVNEEINQALAYIRKADELL-NH2
1022	Biotinyl-SISQVNEEINQSLAYIRKSDELL-NH2
1023	Ac-SISQVNEEINQSLAYIRKSDELL-NH2
1024	Ac-IDISIELNKAKSDLEESKEWIEKSNQELDSIGNWE-NH2
1025	Ac-IDISIELNKAKSDLEESKEWIKKSNQELDSIGNWH-NH2
1026	Ac-IDISIELNKAKSDLEEAKEWIKKANQKLDSIGNWH-NH2
1027	Ac-IDISIELNKAKSDLEESKEWIKKANQKLDSIGNWH-NH2
1028	Ac-IDISIELNKAKSDLEEAKEWIKKSNQKLDSIGNWH-NH2
1029	Biotinyl-NSVALDPIDISIELNKAKSDLEESKEWIKKSNQKL-NH2
1030	Biotinyl-ALDPIDISIELNKAKSDLEESKEWIKKSNQKLDSI-NH2
1031	desAminoTyrosine-NSVALDPIDISIELNKAKSDLEESKEWIKKSNQKL-NH2
1032	desAminoTyrosine-ALDPIDISIELNKAKSDLEESKEWIKKSNQKLDSI-NH2
1033	Ac-YDASISQVNEEINQALAFIRKADEL-NH2
1034	Ac-YDASISQVNEEINQSLAYIRKADELL-NH2
1035	Biotinyl-YDASISQVNEEINQALAYIRKADELL-NH2
1036	Biotinyl-YDASISQVNEEINQSLAFIRKSDELL-NH2
1037	Ac-YDASISQVNEEINQSLAFIRKSDELL-NH2
1038	Ac-WLEWDREINNYTSLIHSLIEESQNQQEKNEQEL-NH2
1039	Biotinyl-IDISIELNKAKSDLEESKEWIRRSNQKLDSIGNWH-NH2
1044	Ac-YESTQKAFDGITNKVNSVIEKTNTQFEAVGKEFGNLEKR-NH2
1045	Biotin-DEYDASISQVNEKINQSLAFIRKSDELL-NH2
1046	Ac-MEWDREINNYTSLIHSLIEESQNQQEKNEQELL-NH2
1047	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNMYEL-NH2
1048	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNEYEL-NH2
1049	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYEL-NH2
1050	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNMYEL-NH2
1051	Ac-WQEWEQKVRYLEANISQSLEQAQIQQEKNEYELQKL-NH2
1052	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1053	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNMYELQKL-NH2
1054	Ac-IDISIELNKAKSDLEESKEWIEKSNQKLDSIGNWH-NH2
1055	Ac-EFGNLEKRLENLNKRVEDGFLDVWTYNAELLVALENE-NH2
1056	Ac-EDGFLDVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQL-NH2
1057	Ac-SISQVNEKINQSLAFIRKSDELL-NH2
1058	desaminoTyr-SISQVNEKINQSLAFIRKSDELL-NH2
1059	Ac-SISQVNEKINQSLAYIRKSDELL-NH2
1060	Ac-QQLLDVVKRQQEMLRLTVWGTKNLQARVTAIEKYLKDQ-NH2
1061	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFC
1062	Ac-FDASISQVNEKINQSLAYIRKSDELL-NH2
1063	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWA
1064	Indole-3-acetyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1065	Indole-3-acetyl-DEFDESISQVNEKINQSLAFIRKSDELL-NH2
1066	Indole-3-acetyl-DEFDESISQVNEKIEQSLAFIRKSDELL-NH2
1067	Indole-3-acetyl-DEFDESISQVNEKIEESLAFIRKSDELL-NH2
1068	Indole-3-acetyl-DEFDESISQVNEKIEESLQFIRKSDELL-NH2
1069	Indole-3-acetyl-GGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1070	2-Napthoyl-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1071	desNH2Tyr-DEFDASISQVNEKINQSLAFIRKSDELL-NH2
1072	biotin-ALDPIDISIELNKAKSDLEESKEWIRRSNQKLDSI-NH2
1073	Ac-YDASISQVNEKINQALAYIRKADELLHNVNAGKST-NH2

T. No.	Sequence
1074	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELLHNV-NH2
1075	Ac-VYPSDEYDASISQVNEKINQSLAYIRKSDELLHNV-NH2
1076	Ac-WGWGYGYG-NH2
1077	Ac-YGWGWGWGF-NH2
1078	Ac-WQEWEQKVRYLEANITALQEQAQIQAEKAEYELQKL-NH2
1079	Ac-WQEWEQKVRYLEAEITALQEEAQIQAEKAEYELQKL-NH2
1081	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWAS
1082	Ac-VWPSDEFDASISQVNEKINQSLAFIRKSDELLHNV-NH2
1083	Ac-SKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDWGV-NH2
1084	Ac-LSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDWG-NH2
1085	Ac-DLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSDW-NH2
1086	Ac-EDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTSD-NH2
1087	Ac-IEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWTS-NH2
1088	Ac-GIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWWT-NH2
1089	Ac-IGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKWW-NH2
1090	2-Napthoyl--PSDEFDASISQVNEKINQSLAFIRKSDELLHNVN-NH2
1091	Ac-VYPSDEYDASISQVNEKINQALAYIRKADELLENV-NH2
1092	Ac-VYPSDEFDASISQVNEKINQALAFIRKADELLENV-NH2
1093	Ac-VYPSDEYDASISQVNEKINQALAYIREADELLENV-NH2
1094	Biotinyl-YDASISQVNEKINQSLAFIRESDELL-NH2
1095	Ac-AIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGKW-NH2
1096	Ac-AAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGGK-NH2
1097	Ac-DAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLGG-NH2
1098	Ac-PDAAIGIEDLSKNISEQIDQIKKDEQKEGTGWGLG-NH2
1099	Ac-NITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQWI-NH2
1100	Ac-KNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQW-NH2
1101	Ac-TKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWRQ-NH2
1102	Ac-WTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGWR-NH2
1103	Ac-DWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTGW-NH2
1104	Ac-HDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWTG-NH2
1105	Ac-PHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWWT-NH2
1106	Ac-EPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNWW-NH2
1107	Ac-IEPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDNW-NH2
1108	Ac-AIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDNDN-NH2
1109	Ac-AAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDND-NH2
1110	Ac-DAAIEPHDWTKNITDKIDQIIHDFVDKTLPDQGDN-NH2
1111	Ac-LSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIFF-NH2
1112	Ac-GLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPIF-NH2
1113	Ac-VGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLPI-NH2
1114	Ac-FVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLLP-NH2
1115	Ac-WFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPLL-NH2
1116	Ac-QWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLPL-NH2
1117	Ac-VQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFLP-NH2
1118	Ac-FVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPFL-NH2
1119	Ac-PFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSPF-NH2
1120	Ac-VPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILSP-NH2
1121	Ac-LVPFVQWFVGLSPTVWLSVIWMMWYWGPSLYSILS-NH2
1122	H-NNITTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKW-OH
1123	H-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-OH
1124	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLENV-NH2

T No.	Sequence
1125	Ac-VFPSDEFDASISQVNEKINQSLAYIREADELLENV-NH2
1126	Ac-DEFDASISQVNEKINQSLAYIREADELL-NH2
1127	Ac-NEQELLELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1128	Ac-LELDKWASLWNWFGGGGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1129	2-Naphthoyl-EGEGEGEGDEFDASISQVNEKINQSLAFIRKSDELL-NH2
1130	Ac-ASRKCRAKFKQLLQHYREVAAAKSSENDRLRLLLKQMCPSLDV-NH2
1131	2-Naphthoyl-GDEEDASISQVNEKINQSLAFIRKSDELL-NH2
1132	2-Naphthoyl-GDEEDASESQVNEKINQSLAFIRKSDELL-NH2
1133	2-Naphthoyl-GDEEDASESQQNEKINQSLAFIRKSDELL-NH2
1134	2-Naphthoyl-GDEEDASESQQNEKQNQSLAFIRKSDELL-NH2
1135	2-Naphthoyl-GDEEDASESQQNEKQNQSEAFIRKSDELL-NH2
1136	Ac-WGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1137	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1138	Ac-YTSLIHSLGGDEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH2
1139	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1140	2-Naphthoyl-GDEEDESISQVNEKIEESLAFIRKSDELL-NH2
1141	2-Naphthoyl-GDEEDESISQVQEKIEESLAFIRKSDELL-NH2
1142	2-Naphthoyl-GDEEDESISQVQEKIEESLLFIRKSDELL-NH2
1143	Biotin-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
1144	2-Naphthoyl-GDEYDESISQVNEKIEESLAFIRKSDELL-NH2
1145	Ac-YTSLIHSLIDEQEKIEELAFIRKSDELLELDKWNWF-NH2
1146	VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1147	Ac-NNLLRAIEAQQHLLQLTVWGSKQLQARILAVERYLKDQ-NH2
1148	GGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1149	Ac-NNLLRAIEAQQHLLQLTVWGEKQLQARILAVERYLKDQ-NH2
1150	Ac-PTRVNYILIIGVLVLAbuEVTGVRADVHLL-NH2
1151	Ac-PTRVNYILIIGVLVLAbuEVTGVRADVHLLEQPGNLW-NH2
1152	Ac-PEKTPLLPTRVNYILIIGVLVLAbuEVTGVRADVHLL-NH2
1153	AhxGGGVYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1155	Ac-YTSLIHSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1156	Ac-YTSLGGDEFDESISQVNEKIEESLAFIRKSDELL-NH2
1157	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWASLWNWF-NH2
1158	Ac-DEFDESISQVNEKIEESLAFIRKSDELLGGWNWF-NH2
1159	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1160	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKSLWNWF-NH2
1161	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKLWNWF-NH2
1162	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWNWF-NH2
1163	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKASLWNWF-NH2
1164	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKSLWNWF-NH2
1165	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKLWNWF-NH2
1166	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWNWF-NH2
1167	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWN-NH2
1168	Ac-MTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASL-NH2
1169	(Pyr)HWSY(2-napthyl-D-Ala)LRPG-NH2
1170	Ac-WNWFDEFDESISQVNEKIEESLAFIRKSDELLWNWF-NH2
1171	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKYASLYNYF-NH2
1172	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKYAYLYNYF-NH2
1173	2-Naphthoyl-AcaAcaAcaDEFDESISQVNEKIEESLAFIRKSDELLAcaAcaAcaW-NH2
1174	2-Naphthoyl-AcaAcaAcaGDEFDESISQVNEKIEESLAFIRKSDELLGAcaAcaAcaW-NH2
1175	2-Naphthoyl-GDEFDESISQVNEKIEESLAFRRESDELL-NH2

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1176	2-Naphthoyl-GDEFDESISQVNEKIEESLAFIEESDELL-NH2
1177	Ac-WQEWEQKVNYLEANITALLEQAQIQQEKNEYELQKL-NH2
1178	Ac-WQEWEQKVDYLEANITALLEQAQIQQEKNEYELQKL-NH2
1179	Ac-WQEWEQKVRWLEANITALLEQAQIQQEKNEYELQKL-NH2
1180	Ac-WQEWEKQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1181	Ac-WQEWEHQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1182	Ac-WQEWEHKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1183	Ac-WQEWDREVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1184	Ac-WQEWEREVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1185	Ac-WQEWERQVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1186	Ac-WQEWEQKVKYLEANITALLEQAQIQQEKNEYELQKL-NH2
1187	Ac-WQEWEQKVRFLEANITALLEQAQIQQEKNEYELQKL-NH2
1188	Ac-VNalPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1189	Ac-VNalPSDENalDASISQVNEEINQALAYIRKADELLENV-NH2
1190	Ac-VNalPSDEYDASISQVNEEINQALANalIRKADELLENV-NH2
1191	Ac-VYPSDEFDASISQVNEKINQSLAFIREADELLFNFF-NH2
1192	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLFNFF-NH2
1193	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1194	Ac-YTSLITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1195	Ac-YTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
1196	Ac-YTSLITALLEQAQIQQEKNEYELQELDEWASLWEWF-NH2
1197	Ac-YTSLITALLEEAQIQQEKNEYELQELDEWASLWEWF-NH2
1198	Naphthoyl-Aua-Aua-Aua-TALLEQAQIQQEKNEYELQKLAua-Aua-Aua-W-NH2
1199	Ac-WAAWEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1200	Ac-WQEAAQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1201	Ac-WQEWAAKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1202	Ac-WQAAEQKVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1203	Ac-WQEWEAAVRYLEANITALLEQAQIQQEKNEYELQKL-NH2
1204	Ac-WQEWEQAARYLEANITALLEQAQIQQEKNEYELQKL-NH2
1205	Ac-WQEWEQKAAYLEANITALLEQAQIQQEKNEYELQKL-NH2
1206	Ac-WQEWEQKVAALEANITALLEQAQIQQEKNEYELQKL-NH2
1207	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKLGGGGWASLWNF-NH2
1208	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELT-NH2
1209	2-Naphthoyl-GDEFDASISQVNEKINQSLAFTRKSDELT-NH2
1210	2-Naphthoyl-GDEFDASISQVNEKTNQSLAFTRKSDELT-NH2
1211	2-Naphthoyl-GDEFDASISQTNEKTNQSLAFTRKSDELT-NH2
1212	2-Naphthoyl-GDEFDASTSQTNEKTNQSLAFTRKSDELT-NH2
1213	2-Naphthoyl-GDEYDASTSQTNEKTNQSLAFTRKSDELT-NH2
1214	2-Naphthoyl-GDEFDEEISQVNEKIEESLAFIRKSDELL-NH2
1215	2-Naphthoyl-GDEFDASISQVNEKINQSLAFIRKSDELA-NH2
1216	2-Naphthoyl-GDEFDASASQANEKANQSLAFARKSDELA-NH2
1217	2-Naphthoyl-GDEFDESISQVNEKIEESLAFTRKSDELL-NH2
1218	2-Naphthoyl-GDEFDESISQVNEKTEESLAFIRKSDELL-NH2
1219	2-Naphthoyl-GDEFDESISQTNEKIEESLAFIRKSDELL-NH2
1220	2-Naphthoyl-GDEFDESTSQVNEKIEESLAFIRKSDELL-NH2
1221	Ac-WNWFDEFDESTSQVNEKIEESLAFIRKSDELLWNWF-NH2
1222	Ac-WNWFDEFDESTSQTNEKIEESLAFIRKSDELLWNWF-NH2
1223	Ac-WNWFDEFDESTSQTNEKTEESLAFIRKSDELLWNWF-NH2
1224	Ac-LQAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVAL-NH2
1225	Ac-YTHLIYTLLEESQNQQEKNEQELLELDKWASLWSWF-NH2

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1226	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1227	Ac-NNMTWQEWEQKVRYLEANITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1230	Ac-WNWFIEESDELLWNWF-NH2
1231	2-Naphthoyl-GFIEESDELLW-NH2
1232	Ac-WFIEESDELLW-NH2
1233	2-Naphthoyl-GFNFFIEESDELLFNFF-NH2
1234	2-Naphthoyl-GESDELW-NH2
1235	Ac-WNWFGDEFDESISQVQEEIEESLAFIEESDELLGGWNWF-NH2
1236	Ac-WNWFIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1237	Ac-YTSLITALLEQAQIQQEENEYELQELDEWASLWEWF-NH2
1238	Ac-YTSLIHSLGGDEFDESISQVNEEIEESLAFIEESDELLGGWASLWNWF-NH2
1239	2-Naphthoyl-GDEFDESISQVQEEIEESLAFIEESDELL-NH2
1240	H-QARQLLSSIMQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-OH
1241	Ac-CPKYVKQNTLKLATGMRNVPEKQTR-NH2
1242	Ac-GLFGAIAGFIENGWEGMIDGWYGFRHQNSC-NH2
1243	Ac-LNFLGGT-NH2
1244	Ac-LDSWWTSLNFLGGT-NH2
1245	Ac-ILTIPQSLDSWWTSLNFLGGT-NH2
1246	Ac-GFFLLTRILTIPQSLDSWWTSLNFLGGT-NH2
1247	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1248	Ac-WNWFITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1249	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1250	Ac-WQEWEQKVRYLEANITALLEQAQIQQEKIEYELQKL-NH2
1251	Ac-WQEWEQKVRYLEAQITALLEQAQIQQEKIEYELQKL-NH2
1252	Ac-KENKANGTDAKVKLIKQELDKYKNAVTELQLLMQS-NH2
1253	Ac-NIKENKANGTDAKVKLIKQELDKYKNAVTELQLLM-NH2
1254	(FS)-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1255	2-Naphthoyl-GWNWFAcaDEFDESISQVQEEIEESLAFIEESDELLAcaWNWF-NH2
1256	Ac-WNWFGDEFDESISQVNEKIEESLAFIEESDELLGWNWF-NH2
1257	Ac-WNWFGDEFDESISQVNEKIEESLAFIRKSDELLGWNWF-NH2
1258	Ac-WNWF-Aca-DEFDESISQVNEKIEESLAFIRKSDELL-Aca-WNWF-NH2
1259	Ac-WNWF-Aca-DEFDESISQVNEKIEESLAFIEESDELL-Aca-WNWF-NH2
1260	Ac-EESQNQQEKNEQELLELDKWA-NH2
1261	EESQNQQEKNEQELLELDKWA
1262	Ac-CGTTDRSGAPTYSWGANDTDVFVLNNTRPPLGNWFG-NH2
1263	Ac-GVEHRLEAACNWTRGERADLEDRDRSELSP-NH2
1264	Ac-CVREGNASRAWVAVTPTVATRDGKLPT-NH2
1265	Ac-CFSPRHHWTTQDANASIYPG-NH2
1266	Ac-LQHYREVAAAKSSENDRLRLLLKQMCPSLDVDS-NH2
1267	Ac-WQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
1268	Ac-CWQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWASLWEWFC-NH2
1269	Ac-WQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1270	Ac-CWQEWDREISNYTSLITALLEQAQIQQEKNEYELQKLDEWEWFC-NH2
1271	Ac-GQNSQSPTSNHSPTSAPPTAPGYRWA-NH2
1272	Ac-PGSSTTSTGPARTALTTAQGTSLYPSA-NH2
1273	Ac-PGSSTTSTGPARTALTTAQGTSLYPSAAATKPSDGNATA-NH2
1275	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDKWASLWNWF-NH2
1276	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDEWASLWEWF-NH2
1277	Ac-WQEWDREITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1278	Ac-WQEWEREITALLEQAQIQQEKIEYELQKLIEWEWF-NH2

T No.	Sequence
1279	Ac-WQEWEREITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1280	Ac-WQEWEREITALLEQAQIQQEKIEYELQKLDEWEWF-NH2
1281	Ac-WQEWEITALLEQAQIQQEKNEYELQKLDEWEWF-NH2
1282	Ac-WQEWEITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1283	Ac-WQEWEITALLEQAQIQQEKIEYELQKLDEWEWF-NH2
1284	Ac-WQEWEITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
1285	Ac-WQEWDREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1286	Ac-WQEWEREIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1287	Ac-WQEWEIDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1288	Ac-WQEWDREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1289	Ac-WQEWEREIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1290	Ac-WQEWEIDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1291	Ac-WQEWDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1292	Ac-WQEWDEYDASISQVNEEINQALAYIREADELWEWF-NH2
1293	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
1294	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
1295	Ac-WQEWEITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
1298	-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1299	Ac-WVYPSDEYDASISQVNEEINQALAYIRKADELLENVWNWF-NH2
1300	YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1301	Ac-WQEWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
1302	Ac-WQAWDEYDASISQVNEKINQALAYIREADELWAWF-NH2
1303	Ac-WQAWDEYDASISQVNEKINQALAYIREADELWEWF-NH2
1304	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAFIRKSDEL-NH2
1305	Biotin-YDPLVFPSDEFDASISQVNEKINQSLAF-NH2
1306	Biotin-QVNEKINQSLAFIRKSDELLHNVNAGKST-NH2
1307	Ac-WMEWDREI-NH2
1308	Ac-WQEWEQKI-NH2
1309	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIKWASLWEWF-NH2
1310	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLIEWASLWEWF-NH2
1311	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKLIEWEWF-NH2
1312	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKEWEWF-NH2
1313	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKEWEW-NH2
1314	Ac-WQEWEREISAYTSLITALLEQAQIQQEKIEYELQKLIEWEW-NH2
1315	Ac-FNLSDHSESIQKKFQLMKKHVNKIGVDSDPIGSWLR-NH2
1316	Ac-DHSESIQKKFQLMKKHVNKIGVDSDPIGSWLRGIF-NH2
1317	Ac-WSVKQANLTTSLLGDLLDDVTSIRHAVLQNRA-NH2
1318	Biotin-WMEWDREI-NH2
1319	Biotin-NNMTWMEWDREINNYTSL-NH2
1320	Ac-GAASLTLTVQARQLLSGIVQQQNNLLRAIEAQQHLL-NH2
1321	Ac-ASLTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQL-NH2
1322	Ac-VSVGNTLYYVNKQEGKSLYVKGEPIINFYDPLVF-NH2
1323	Ac-QHWSYGLRPG-NH2
1324	Ac-WQEWEQKIQHWSYGLRPGWASLWEWF-NH2
1325	Ac-WQEWEQKIQHWSYGLRPGWEWF-NH2
1326	Ac-WNWFQHWSYGLRPGWNWF-NH2
1327	Ac-FNFFQHWSYGLRPGFNFF-NH2
1328	Ac-GAGAQHWSYGLRPGAGAG-NH2
1329	PLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGGT
1330	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLAKWASLWEWF-NH2

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1331	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLAEWASLWEWF-NH2
1332	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWASLWEWF-NH2
1333	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWASLWAWF-NH2
1334	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAKWASLWAWF-NH2
1335	Ac-THKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNK-NH2
1336	Ac-KAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQS-NH2
1337	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWEWF-NH2
1338	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLIEWEWF-NH2
1339	Ac-WQEWEQKITALLEQAQIQQEKIEYELQKLDKWEWF-NH2
1340	Ac-YDPLVFPSDEFDASISQVNEKINQSLAF-NH2
1341	Fluor--VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1342	Fluor-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1344	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARIL-NH2
1345	Ac-QQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
1346	Ac-SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQ-NH2
1347	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAWF-NH2
1348	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWASLWAW-NH2
1349	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWASLWAW-NH2
1350	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWAGLWAWF-NH2
1351	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAEWAGLWAW-NH2
1352	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLAEWAGLWAW-NH2
1353	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWAGLWEWF-NH2
1354	Ac-WQEWQHWSYGLRPGWEWF-NH2
1355	Ac-WQAWQHWSYGLRPGWAWF-NH2
1356	Biotinyl-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1357	WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF
1358	WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF
1361	Ac-AGSTMGARSMTLTVQARQLLSGIVQQQNNLLRAIEAQQ-NH2
1362	Ac-AGSAMGAASLTLSAQSRTLLAGIVQQQQQLLDVVKRQQ-NH2
1363	Ac-AGSAMGAASTALTAQSRTLLAGIVQQQQQLLDVVKRQQ-NH2
1364	Ac-ALTAQSRTLLAGIVQQQQQLLDVVKRQQELLRLTVWGT-NH2
1365	Ac-TLSAQSRTLLAGIVQQQQQLLDVVKRQQEMLRLTVWGT-NH2
1366	Ac-TLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGI-NH2
1367	Ac-WQAWIEYEAELSQVKEKIEQSLAYIREADELWAWF-NH2
1368	Ac-WQAWIEYEASLSQAKEKIEESKAYIREADELWAWF-NH2
1369	Ac-WQAWIEYERLLVQAKLKIAIAKLYIAKELLEWAWF-NH2
1370	Ac-WQAWIEYERLLVQVKLKIAIALLYIAKELLEWAWF-NH2
1371	Ac-WQAWIELERLLVQVKLKLAIAKLEIAKELLEWAWF-NH2
1372	Ac-GEWTYDDATKTFTVTEGGH-NH2
1373	Ac-WQEWEQKIGEWTYDDATKTFTVTEGGHWASLWEWF-NH2
1374	Ac-GEWTYDDATKTFTVTE-NH2
1375	Ac-WQEWEQKIGEWTYDDATKTFTVTEWASLWEWF-NH2
1376	Ac-MHRFDYRT-NH2
1377	Ac-WQEWEQKIMHRFDYRTWASLWEWF-NH2
1378	Ac-MHRFNWSTGGG-NH2
1379	Ac-WQEWEQKIMHRFNWSTGGGWASLWEWF-NH2
1380	Ac-MHRFNWST-NH2
1381	Ac-WQEWEQKIMHRFNWSTWASLWEWF-NH2
1382	Ac-LLVPLARIMTIKSSVHGGG-NH2
1383	Ac-WQEWEQKILLVPLARIMTIKSSVHGGGWASLWEWF-NH2

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1384	Ac-LLVPLARIMTMSSVH-NH2
1385	Ac-WQEWEQKILLVPLARIMTMSSVHWASLWEWF-NH2
1386	TALLEQAQIQQEKNEYELQKLDK
1387	Ac-TALLEQAQIQQEKNEYELQKLDK-NH2
1388	Ac-TALLEQAQIQQEKIEYELQKLIE-NH2
1389	TALLEQAQIQQEKIEYELQKLIE
1390	Ac-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
1391	Rhod-QARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERY-NH2
1392	Ac-GAASLTLSAQSRTLLAGIVQQQQQLLDVVKRQQEML-NH2
1393	Ac-GSAMGAASLTLSAQSRTLLAGIVQQQQQLLDVVKRQQEML-NH2
1394	Ac-PALSTGLIHLHQNIVDVQFLFGVGSSIASWAIKWEY-NH2
1395	Ac-PALSTGLIHLHQNIVDVQFLYGVGSSIASWAIK-NH2
1396	Ac-LSTTQWQVLPUSFTTLPALSTGLIHLHQNIVDVQY-NH2
1397	Ac-FRKFPEATFSRUGSGPRITPRUMVDFPFRLWHY-NH2
1398	Ac-DFPFRLWHFPUTINYTIFKVRLFVGGVEHRLEAAUNWTR-NH2
1399	Ac-YVGGVEHRLEAAUNWTRGERUDLEDRDRSELSPL-NH2
1400	MVYPSDEYDASISQVNEEINQALAYIRKADELLENV
1402	Ac-GPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLGG-NH2
1403	Ac-LGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFLG-NH2
1404	Ac-FLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFL-NH2
1405	Ac-YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF-NH2
1406	YTNTIYTLLEESQNQQEKNEQELLELDKWASLWNWF
1407	Ac-YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF-NH2
1408	YTGIIYNLLEESQNQQEKNEQELLELDKWANLWNWF
1409	Ac-YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF-NH2
1410	YTSLIYSLLEKSQIQQEKNEQELLELDKWASLWNWF
1411	Ac-EKSQIQQEKNEQELLELDKWA-NH2
1412	EKSQIQQEKNEQELLELDKWA
1413	Ac-EQAQIQQEKNEYELQKLDKWA-NH2
1414	EQAQIQQEKNEYELQKLDKWA
1415	Ac-YTXLIHSLIXESQNQQXKNEQELXELDKWASLWNWF-NH2
1416	Ac-YTXLIHSLIXESQNQQXKNEQELXELD-NH2
1417	Ac-YTSLIHSLIEESQNQQEKNEQELLELD-NH2
1418	Ac-WQEWEXKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2
1419	Ac-XKITALLXQAQIQQXKNEYELXKLDKWASLWEWF-NH2
1420	Ac-WQEWEXKITALLXQAQIQQXKNEYELXKLD-NH2
1421	Ac-WEQKITALLEQAQIQQEKNEYELQKLD-NH2
1422	Ac-WEXKITALLXQAQIQQXKNEYELXKLD-NH2
1423	Ac-XKITALLXQAQIQQXKNEYELXKLD-NH2
1425	Ac-QKITALLEQAQIQQEKNEYELQKLD-NH2
1426	Ac-QKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1427	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLD-NH2
1428	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEN-OH
1429	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLE-OH
1430	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELL-OH
1431	Ac-VYPSDEYDASISQVNEEINQALAYIRKADEL-OH
1432	YPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1433	PSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1434	SDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1435	DEYDASISQVNEEINQALAYIRKADELLENV-NH2

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1436	Ac-VYPSDEYDASISQVDEEINQALAYIRKADELLENV-NH2
1437	Ac-VYPSDEYDASISQVNEEIDQALAYIRKADELLENV-NH2
1438	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLEDV-NH2
1439	Ac-VYPSDEYDASISQVDEEIDQALAYIRKADELLENV-NH2
1440	Ac-LLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLP-NH2
1441	Ac-LSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPI-NH2
1442	Ac-STNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIV-NH2
1443	Ac-TNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVN-NH2
1444	Ac-NKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNK-NH2
1445	Ac-KAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQ-NH2
1446	Ac-AVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQS-NH2
1447	Ac-VVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSU-NH2
1448	Ac-VSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUS-NH2
1449	Ac-SLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSI-NH2
1450	Ac-LSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSIS-NH2
1451	Ac-SNGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSISN-NH2
1452	Ac-NGVSVLTSKVLDLKNYIDKQLLPIVNKQSUSISNI-NH2
1453	Ac-GVSVLTSKVLDLKNYIDKQLLPIVNKQSUSISNIE-NH2
1454	Ac-VSVLTSKVLDLKNYIDKQLLPIVNKQSUSISNIET-NH2
1455	Ac-SVLTSKVLDLKNYIDKQLLPIVNKQSUSISNIETV-NH2
1456	Ac-VLTSKVLDLKNYIDKQLLPIVNKQSUSISNIETVI-NH2
1457	Ac-LTSKVLDLKNYIDKQLLPIVNKQSUSISNIETVIE-NH2
1458	Ac-TSKVLDLKNYIDKQLLPIVNKQSUSISNIETVIEF-NH2
1459	Ac-SKVLDLKNYIDKQLLPIVNKQSUSISNIETVIEFQ-NH2
1460	Ac-KVLDLKNYIDKQLLPIVNKQSUSISNIETVIEFQQ-NH2
1461	Ac-VLDLKNYIDKQLLPIVNKQSUSISNIETVIEFQQK-NH2
1462	Ac-LDLKNYIDKQLLPIVNKQSUSISNIETVIEFQQKN-NH2
1463	Ac-DLKNYIDKQLLPIVNKQSUSISNIETVIEFQQKNN-NH2
1464	Ac-LKNYIDKQLLPIVNKQSUSISNIETVIEFQQKNNR-NH2
1465	Ac-KNYIDKQLLPIVNKQSUSISNIETVIEFQQKNNRL-NH2
1466	Ac-NYIDKQLLPIVNKQSUSISNIETVIEFQQKNNRLL-NH2
1467	Ac-YIDKQLLPIVNKQSUSISNIETVIEFQQKNNRLLE-NH2
1468	Ac-IDKQLLPIVNKQSUSISNIETVIEFQQKNNRLLEI-NH2
1469	Ac-DKQLLPIVNKQSUSISNIETVIEFQQKNNRLLEIT-NH2
1470	Ac-KQLLPIVNKQSUSISNIETVIEFQQKNNRLLEITR-NH2
1471	Ac-QLLPIVNKQSUSISNIETVIEFQQKNNRLLEITRE-NH2
1472	Ac-VYPSDEYDASISQVNEEINQALA
1473	QVNEEINQALAYIRKADELLENV-NH2
1474	VYPSDEYDASISQVNEEINQALAYIRKADELLENV
1475	Ac-DEYDASISQVNEEINQALAYIREADEL-NH2
1476	Ac-DEYDASISQVNEKINQALAYIREADEL-NH2
1477	Ac-DDECLNSVKNGTYDFPKFEEESKLNRNEIKGVKLS-NH2
1478	Ac-DDE-Abu-LNSVKNGTYDFPKFEEESKLNRNEIKGVKLS-NH2
1479	Ac-YHKCDDECLNSVKNGTFDFPKFEEESKLNRNEIKGVKLSS-NH2
1480	Ac-YHK-Abu-DDE-Abu-LNSVKNGTFDFPKFEEESKLNRNEIKGVKLSS-NH2
1481	Ac-YTSLIHSLIEESQIQQEKNEQELLELDKWASLWNWF-NH2
1482	Ac-YTSLIHSLIEESQNQQEKNEYELLELDKWASLWNWF-NH2
1483	Ac-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWNWF-NH2
1484	Ac-YTSLIHSLIEESQ[illegible]
1485	Ac-YTSLIHSLIEESQ[illegible]

T. No.	Sequence
1486	Ac-YTSLIHSLIEESQNQQEKNEYELQKLDKWASLWNWF-NH2
1487	Ac-YTSLIHSLIEESQIQQEKNEQELQKLDKWASLWNWF-NH2
1488	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWEWF-NH2
1489	Ac-YTSLIHSLIEESQIQQEKNEQELLELDKWASLWEWF-NH2
1490	Ac-YTSLIHSLIEESQNQQEKNEYELLELDKWASLWEWF-NH2
1491	Ac-YTSLIHSLIEESQIQQEKNEYELLELDKWASLWEWF-NH2
1492	Ac-YTSLIHSLIEESQIQQEKNEYELQKLDKWASLWEWF-NH2
1493	Ac-YTSLIHSLIEESQNQQEKNEQELQKLDKWASLWEWF-NH2
1494	Ac-YTSLIHSLIEESQNQQEKNEYELQKLDKWASLWEWF-NH2
1495	Ac-YTSLIHSLIEESQIQQEKNEQELQKLDKWASLWEWF-NH2
1496	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWEWF-NH2
1497	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWASLWEWF-NH2
1498	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWASLWEWF-NH2
1499	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWASLWEWF-NH2
1500	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWAGLWEWF-NH2
1501	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWAGLWEWF-NH2
1502	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWAGLWEWF-NH2
1503	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIEWAGLWAWF-NH2
1504	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLAKWAGLWAWF-NH2
1505	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLIKWAGLWAWF-NH2
1506	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLDKWEWF-NH2
1507	Ac-WQEWEQKITALLEQAQIQQEKGEYELLELDKWEWF-NH2
1508	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLAKWEWF-NH2
1509	Ac-WQEWEQKITALLEQAQIQQEKGEYELQKLDEWEWF-NH2
1510	Ac-WQEWEQKITALLEQAQIQQEKGEYELLELAKWEWF-NH2
1511	Ac-WQEWEQKITALLEQAQIQQEKNEYELLELDKWEWF-NH2
1512	Ac-WQEWEQKITALLEQAQIQQEKNEYELLELIEWASLWEWF-NH2
1513	Ac-WQEWEQKITALLEQAQIQQEKNEYELLELIEWAGLWEWF-NH2
1514	Ac-WQEWEQKITALLEQAQIQQEKNEYELLELIEWAGLWAWF-NH2
1515	Ac-WQEWEREITALLEQAQIQQEKNEYELQKLIEWASLWEWF-NH2
1516	Ac-WQEWEREIQQEKNEYELQKLDKWASLWEWF-NH2
1517	Ac-WQEWEREIQQEKGEYELQKLIEWEWF-NH2
1518	Ac-WQEWQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1519	Ac-WQEWQAQIQQEKGEYELQKLIEWEWF-NH2

1520	PEG-GWQEWEQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2
1521	Ac-GWQEWEQRITALLEQAQIQQERNEYELQRLDEWASLWEWF-NH2
1522	PEG-YTSLITALLEQAQIQQERNEQELLELDEWASLWEWF-NH2
1523	Ac-YTSLITALLEQAQIQQERNEQELLELDEWASLWEWF-NH2
1526	PEG-GWQEWEQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2
1527	Ac-GWQEWEQRITALLEQAQIQQERNEYELQELDEWASLWEWF-NH2
1528	PEG-YTSLIGSLIEESQIQQERNEQELLELDRWASLWEWF-NH2
1529	PEG-GWQEWEQRITALLEQAQIQQERNEYELQRLDRWASLWEWF-NH2
1530	Ac-GWQEWEQRITALLEQAQIQQERNEYELQRLDRWASLWEWF-NH2
1531	PEG-GWQEWEQRITALLEQAQIQQERNEYELQELDRWASLWEWF-NH2
1532	Ac-GWQEWEQRITALLEQAQIQQERNEYELQELDRWASLWEWF-NH2
1533	PEG-YTSLIGSLIEESQNQQERNEQELLELDRWASLWNWF-NH2
1534	Ac-YTSLIGSLIEESQNQQERNEQELLELDRWASLWNWF-NH2
1538	Ac-YTSLIHSLIEESQNQQEK-OH
1539	NEQELLELDK
1540	WASLWNWF-NH2
1542	Ac-AAAWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1543	Ac-WQEAAAKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1544	Ac-WQEWEQAAAALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1545	Ac-WQEWEQKITAAAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1546	Ac-WQEWEQKITALLAAAQIQQEKNEYELQKLDKWASLWEWF-NH2
1547	Ac-WQEWEQKITALLEQAAAAQEKNEYELQKLDKWASLWEWF-NH2
1548	Ac-WQEWEQKITALLEQAQIQAAANEYELQKLDKWASLWEWF-NH2
1549	Ac-WQEWEQKITALLEQAQIQQEKAAAELQKLDKWASLWEWF-NH2
1550	Ac-WQEWEQKITALLEQAQIQQEKNEYAAAKLDKWASLWEWF-NH2
1551	Ac-WQEWEQKITALLEQAQIQQEKNEYELQAAAKWASLWEWF-NH2
1552	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDAAASLWEWF-NH
1553	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWAAAAEWF-NH
1554	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWAAA-NH
1556	Ac-YTSLIHSLIEESQNQQEKNEQELLLDKWASLWNWF-NH2
1557	Ac-YTSLIHSLIEESQNQEKNEQELLELDKWASLWNWF-NH2
1558	Ac-ERTLDFHDS-NH2
1559	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWN(W)F-NH2
1563	Ac-YTSLIHSLIEESQN(Q)QEKNEQELLELDKWASLWNWF-NH2
1564	Ac-YTSLIHSLIEESQNQQDKWASLWNWF-NH2
1566	Ac-FYEIIMDIEQNNVQGKKGIQQLQKWEDWVGWIGNI-NH2
1567	Ac-INQTIWNHGNITLGEWYNQTKDLQQKFYEIIMDIE-NH2
1568	Ac-WNHGNITLGEWYNQTKDLQQKFYEIIMDIEQNNVQ-NH2
1572	Ac-YTSLIHSLIEESENQQEKNEQELLELDKWASLWNWF-NH2
1573	Ac-YTSLIHSLIEESQDQQEKNEQELLELDKWASLWNWF-NH2
1574	Ac-YTSLIHSLIEESQNEQEKNEQELLELDKWASLWNWF-NH2
1575	c-YTSLIHSLIEESQNQEEKNEQELLELDKWASLWNWF-NH2
1576	Ac-YTSLIHSLIEESQNQQEKDEQELLELDKWASLWNWF-NH2
1577	Ac-LGEWYNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQ-NH2
1578	Ac-WYNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQLQK-NH2
1579	Ac-YTSLIHSLIEESQNQQEKNEEELLELDKWASLWNWF-NH2
1580	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWDWF-NH2
1586	Ac-XTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWX-NH2
1588	Ac-YNQTKDLQQKFYEIIMDIEQNNVQGKKGIQQLQKW-NH2
1598	Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF
1600	Ac-TLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQAR-NH2
1603	Ac-LQQKFYEIIMDIEQNNVQGKKGIQQLQKWEDWVGW-NH2
1627	Ac-YTSLIHSLIEESQNQQEKNEQELLALDKWASLWNWF-NH2
1628	Ac-YTSLIHSLIEESQNQQEKNEQELLEADKWASLWNWF-NH2

1629	Ac-YTSLIHSLIEESQNQQEKNEQELLELAKWASLWNWF-NH2
1630	Ac-YTSLIHSLIEESQNQQEKAEQELLELDKWASLWNWF-NH2
1631	Ac-YTSLIHSLIEESQNQQEKNAQELLELDKWASLWNWF-NH2
1632	Ac-YTSLIHSLIEESQNQQEKNEAELLELDKWASLWNWF-NH2
1634	Ac-WQEWEQKITALLEQAQIQQEKNEQELQKLDKWASLWEWF-NH2
1635	Ac-WQEWEQKITALLEQAQIQQEKAEYELQKLDKWASLWEWF-NH2
1636	Ac-WQEWEQKITALLEQAQIQQEKNAYELQKLDKWASLWEWF-NH2
1637	Ac-WQEWEQKITALLEQAQIQQEKNEAELQKLDKWASLWEWF-NH2
1644	Ac-EYDLRRWEK-NH2
1645	Ac-EQELLELDK-NH2
1646	Ac-EYELQKLDK-NH2
1647	Ac-WQEWEQKITALLEQAQIQQEKNEQELLKLDKWASLWEWF-NH2
1648	Ac-WQEWEQKITALLEQAQIQQEKNEQELLELDKWASLWEWF-NH2
1649	Ac-WQEWEQKITALLEQAQIQQEKNDKWASLWEWF-NH2
1650	Ac-YTSLIHSLIEESQNQAEKNEQELLELDKWASLWNWF-NH2
1651	Ac-YTSLIHSLIEESQNQQAKNEQELLELDKWASLWNWF-NH2
1652	Ac-YTSLIHSLIEESQNQQEANEQELLELDKWASLWNWF-NH2
1653	Ac-YTSLIHSLIEESANQQEANEQELLELDKWASLWNWF-NH2
1654	Ac-YTSLIHSLIEESQAQQEKNEQELLELDKWASLWNWF-NH2
1655	Ac-YTSLIHSLIEESQNAQEKNEQELLELDKWASLWNWF-NH2
1656	Ac-YTSLIHALIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1657	Ac-YTSLIHSAIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1658	Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH2
1659	Ac-YTSLIHSLAEESQNQQEKNEQELLELDKWASLWNWF-NH2
1660	Ac-YTSAIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1661	Ac-YTSLAHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1662	Ac-YTSLIASLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1663	Ac-ATSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1664	Ac-YASLIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1665	Ac-YTALIHSLIEESQNQQEKNEQELLELDKWASLWNWF-NH2
1666	Ac-RIQDLEKYVEDTKIDLWSYNAELLVALENQ-NH2
1667	Ac-HTIDLTDSEMNKLFEKTRRQLREN-NH2
1668	Ac-SEMNKLFEKTRRQLREN -NH2
1669	Ac-VFPSDEADASISQVNEKINQSLAFIRKSDELLHNV-NH2
1670	Ac-VFPSDEFAASISQVNEKINQSLAFIRKSDELLHNV-NH2
1671	Ac-VFPSDEFDASISAVNEKINQSLAFIRKSDELLHNV-NH2
1672	Ac-VFPSDEFDASISQANEKINQSLAFIRKSDELLHNV-NH2
1673	Ac-VFPSDEFDASISQVAEKINQSLAFIRKSDELLHNV-NH2
1674	Ac-WQEWEQKITAALEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1675	Ac-WQEWEQKITALAEQAQIQQEKNEYELQKLDKWASLWEWF-NH2
1676	Ac-WQEWEQKITALLEQAAIQQEKNEYELQKLDKWASLWEWF-NH2
1677	Ac-WQEWEQKITALLEQAQAQQEKNEYELQKLDKWASLWEWF-NH2
1678	Ac-WQEWEQKITALLEQAQIAQEKNEYELQKLDKWASLWEWF-NH2
1679	Ac-WQEWEQKITALLEQAQIQAEKNEYELQKLDKWASLWEWF-NH2
1680	Ac-VFPSDEFDASISQVNEKINQSAAFIRKSDELLHNV-NH2
1681	Ac-VFPSDEFDASISQVNEKINQSLAAIRKSDELLHNV-NH2
1682	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDEALHNV-NH2
1683	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELAHNV-NH2
1684	Ac-VFPSDEFDASISQVNEKINQSLAFIRKSDELLANV-NH2
1685	Ac-WQEWEQKITALLEQAQIQQAKNEYELQKLDKWASLWEWF-NH2
1687	Ac-WQEWEQKITALLEQAQIQQEKNEYELQALDKWASLWEWF-NH2
1688	Ac-WQEWEQKITALLEQAQIQQEKNEYELQKADKWASLWEWF-NH2

It is to be understood that the peptides listed in Table 2 are also intended to fall within the scope of the present invention. As discussed above, those peptides depicted in Table 2 that do not already contain enhancer peptide sequences (that is, do not represent hybrid polypeptides) can be utilized in connection with the enhancer peptide sequences and teaching provided herein to generate hybrid polypeptides. Further, the core polypeptides and the core polypeptide of the hybrid polypeptides shown in Table 2 and FIG. 13 can be used with any of the enhancer peptide sequences described herein to routinely produce additional hybrid polypeptides, which are also intended to fall within the scope of the present invention.

It is noted that while a number of the polypeptides listed in Table 2 and FIG. 13 are depicted with modified, e.g., blocked amino and/or carboxy termini or d-isomeric amino acids (denoted by residues within parentheses), it is intended that any polypeptide comprising a primary amino acid sequence as depicted to Table 2 and FIG. 13 is also intended to be part of the present invention.

The core polypeptide sequences, per se, shown in Table 2 and FIG. 13, as well as the hybrid polypeptides comprising such core polypeptides, can exhibit antiviral, and/or anti-fusogenic activity and/or can exhibit an ability to modulate interacellular processes that involve coiled-coil peptide structures. Among the core polypeptide sequences are, for example, ones which have been derived from individual viral protein sequences. Also among the core polypeptide sequences are, for example, ones whose amino acid sequences are derived from greater than one viral protein sequence (e.g., an HIV-1, HIV-2 and SIV -derived core polypeptide).

In addition, such core polypeptides can exhibit amino acid substitutions, deletions and/or insertions as discussed, above, for enhancer polypeptide sequences as long as the particular core polypeptide's antiviral and/or antifusogenic activity (either per se or as part of a hybrid polypeptide) is not abolished.

With respect to amino acid deletions, it is preferable that the resulting core polypeptide is at least about 4-6 amino acid residues in length. With respect to amino acid insertions, preferable insertions are no greater than about 50 amino acid residues, and, more preferably no more than about 15 amino acid residues. It is also preferable that core polypeptide insertions be amino- and/or carboxy-terminal insertions.

Among such amino and/or carboxy-terminal insertions are ones which comprise amino acid sequences amino and/or carboxy to the endogenous protein sequence from which the core polypeptide is derived. For example, if the core polypeptide is derived from gp41 protein, such an insertion would comprise an amino and/or carboxy-terminal insertion comprising a gp41 amino acid sequence adjacent to the gp41 core polypeptide sequence. Such amino and/or carboxy terminal insertions can typically range from about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 amino acid residues amino to and/or carboxy to the original core polypeptide.

The hybrid polypeptides of the invention can still further comprise additional modifications that readily allow for detection of the polypeptide. For example, the hybrid polypeptides can be labeled, either directly or indirectly. Peptide labeling techniques are well known to those of skill in the art and include, but are not limited to, radioactive, fluorescent and colorimetric techniques. Indirect labeling techniques are also well known to those of skill in the art and include, but are not limited to, biotin/streptavidin labeling and indirect antibody labeling.

The invention further relates to the association of the enhancer polypeptide sequences to types of molecules other than peptides. For example, the enhancer peptide sequences may be linked to nucleic acid molecules (e.g., DNA or RNA) or any type of small organic molecule for the purpose of enhancing the pharmacokinetic properties of said molecules.

5.2. SYNTHESIS OF PEPTIDES

The enhancer, core and hybrid polypeptides of the invention may be synthesized or prepared by techniques well known in the art. See, for example, Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman and Co., NY, which is incorporated herein by reference in its entirety. Hybrid polypeptides may be prepared using conventional step-wise solution or solid phase synthesis, fragment condensation, F-MOC or T-BOC chemistry. (see, *e.g.*, Chemical Approaches to the Synthesis of Peptides and Proteins, Williams *et al.*, Eds., 1997, CRC Press, Boca Raton Florida, and references cited therein; Solid Phase Peptide Synthesis: A Practical Approach, Atherton & Sheppard, Eds., 1989, IRL Press, Oxford, England, and references cited therein). Likewise the amino- and/or carboxy-terminal modifications.

The enhancer, core and hybrid polypeptides of the invention can be purified by art-known techniques such as normal and reverse phase high performance liquid chromatography, ion exchange chromatography, gel electrophoresis, affinity chromatography, size exclusion, precipitation and the like. The actual conditions used to purify a particular polypeptide will depend, in part, on synthesis strategy and on factors such as net charge, hydrophobicity, hydrophilicity, solubility, stability etc., and will be apparent to those having skill in the art.

Hybrid, enhancer and core polypeptides may also be made using recombinant DNA techniques. Here, the nucleotide sequences encoding the polypeptides of the invention may be synthesized, and/or cloned, and expressed according to techniques well known to those of ordinary skill in the art. See, for example, Sambrook, et al., 1989, Molecular Cloning, A Laboratory Manual, Vols. 1-3, Cold Spring Harbor Press, NY.

One may obtain the DNA segment encoding the polypeptide of interest using a variety of molecular biological techniques, generally known to those skilled in the art. For

example, polymerase chain reaction (PCR) may be used to generate the DNA fragment encoding the protein of interest. Alternatively, the DNA fragment may be obtained from a commercial source.

The DNA encoding the polypeptides of interest may be recombinantly engineered into a variety of host vector systems that also provide for replication of the DNA in large scale. These vectors can be designed to contain the necessary elements for directing the transcription and/or translation of the DNA sequence encoding the hybrid polypeptide.

Vectors that may be used include, but are not limited to, those derived from recombinant bacteriophage DNA, plasmid DNA or cosmid DNA. For example, plasmid vectors such as pcDNA3, pBR322, pUC 19/18, pUC 118, 119 and the M13 mp series of vectors may be used. Bacteriophage vectors may include λgt10, λgt11, λgt18-23, λZAP/R and the EMBL series of bacteriophage vectors. Cosmid vectors that may be utilized include, but are not limited to, pJB8, pCV 103, pCV 107, pCV 108, pTM, pMCS, pNNL, pHSG274, COS202, COS203, pWE15, pWE16 and the charomid 9 series of vectors.

Alternatively, recombinant virus vectors including, but not limited to, those derived from viruses such as herpes virus, retroviruses, vaccinia viruses, adenoviruses, adeno-associated viruses or bovine papilloma viruses plant viruses, such as tobacco mosaic virus and baculovirus may be engineered.

In order to express a biologically active polypeptide, the nucleotide sequence coding for the protein may be inserted into an appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequences. Methods which are well known to those skilled in the art can be used to construct expression vectors having the hybrid polypeptide coding sequence operatively associated with appropriate transcriptional/translational control

signals. These methods include *in vitro* recombinant DNA techniques and synthetic techniques. See, for example, the techniques described in Sambrook, *et al.*, 1992, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y. and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Greene Publishing Associates & Wiley Interscience, N.Y., each of which are incorporated herein by reference in its entirety.

The nucleic acid molecule encoding the hybrid, enhancer and core polypeptides of interest may be operatively associated with a variety of different promoter/enhancer elements. The promoter/enhancer elements may be selected to optimize for the expression of therapeutic amounts of protein. The expression elements of these vectors may vary in their strength and specificities. Depending on the host/vector system utilized, any one of a number of suitable transcription and translation elements may be used. The promoter may be in the form of the promoter which is naturally associated with the gene of interest. Alternatively, the DNA may be positioned under the control of a recombinant or heterologous promoter, *i.e.*, a promoter that is not normally associated with that gene. For example, tissue specific promoter/enhancer elements may be used to regulate the expression of the transferred DNA in specific cell types.

Examples of transcriptional control regions that exhibit tissue specificity which have been described and could be used include, but are not limited to, elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, 1984, Cell 38:639-646; Ornitz *et al.*, 1986, Cold Spring Harbor Symp. Quant. Biol. 50:399-409; MacDonald, 1987, Hepatology 7:42S-51S); insulin gene control region which is active in pancreatic beta cells (Hanahan, 1985, Nature 315:115-122); immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, 1984, Cell

38:647-658; Adams *et al.*, 1985, Nature 318:533-538; Alexander *et al.*, 1987, Mol. Cell. Biol. 7:1436-1444): albumin gene control region which is active in liver (Pinkert *et al.*, 1987, Genes and Devel. 1:268-276) alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.*, 1985, Mol. Cell. Biol. 5:1639-1648; Hammer *et al.*, 1987, Science 235:53-58); alpha-1-antitrypsin gene control region which is active in liver (Kelsey *et al.*, 1987, Genes and Devel. 1:161-171); beta-globin gene control region which is active in myeloid cells (Magram *et al.*, 1985, Nature 315:338-340; Kollias *et al.*, 1986, Cell 46:89-94); myelin basic protein gene control region which is active in oligodendrocyte cells in the brain (Readhead *et al.*, 1987, Cell 48:703-712); myosin light chain-2 gene control region which is active in skeletal muscle (Shani, 1985, Nature 314:283-286); and gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason *et al.*, 1986, Science 234:1372-1378). Promoters isolated from the genome of viruses that grow in mammalian cells, (*e.g.*, vaccinia virus 7.5K, SV40, HSV, adenoviruses MLP, MMTV, LTR and CMV promoters) may be used, as well as promoters produced by recombinant DNA or synthetic techniques.

In some instances, the promoter elements may be constitutive or inducible promoters and can be used under the appropriate conditions to direct high level or regulated expression of the nucleotide sequence of interest. Expression of genes under the control of constitutive promoters does not require the presence of a specific substrate to induce gene expression and will occur under all conditions of cell growth. In contrast, expression of genes controlled by inducible promoters is responsive to the presence or absence of an inducing agent.

Specific initiation signals are also required for sufficient translation of inserted protein coding sequences.

These signals include the ATG initiation codon and adjacent sequences. In cases where the entire coding sequence, including the initiation codon and adjacent sequences are inserted into the appropriate expression vectors, no additional translational control signals may be needed. However, in cases where only a portion of the coding sequence is inserted, exogenous translational control signals, including the ATG initiation codon must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the protein coding sequences to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of transcription attenuation sequences, enhancer elements, etc.

5.3. USES OF THE ENHANCER PEPTIDE SEQUENCES, CORE POLYPEPTIDES AND HYBRID POLYPEPTIDES OF THE INVENTION

As discussed above, the enhancer peptide sequences of the invention can be utilized to enhance the pharmacokinetic properties of any core polypeptide through linkage of the core polypeptide to the enhancer peptide sequences to form hybrid polypeptides. The observed enhancement of pharmacokinetic properties is relative to the pharmacokinetic properties of the core polypeptide alone. Standard pharmacokinetic character parameters and methods for determining and characterizing the pharmacokinetic properties of an agent such as a polypeptide are well known to those of skill in the art. Non-limiting examples of such methods are presented in the Examples provided below.

The enhancer peptide sequences of the invention can, additionally, be utilized to increase the in vitro or ex-vivo half-life of a core polypeptide to which enhancer peptide sequences have been attached. For example, enhancer peptide sequences can increase the half life of attached core polypeptides when the resulting hybrid polypeptides are

present in cell culture, tissue culture or patient samples, (e.g., cell samples, tissue samples biopsies, or other sample containing bodily fluids).

The core polypeptides and hybrid polypeptides of the invention can also be utilized as part of methods for modulating (e.g., decreasing, inhibiting, disrupting, stabilizing or enhancing) fusogenic events. Preferably, such peptides exhibit antifusogenic or antiviral activity. The peptides of the invention can also exhibit the ability to modulate intracellular processes involving coiled-coil peptide interactions.

In particular embodiments, the hybrid polypeptides and core polypeptides of the invention that exhibit antiviral activity can be used as part of methods for decreasing viral infection. Such antiviral methods can be utilized against, for example, human retroviruses, particularly HIV (human immunodeficiency virus), e.g., HIV-1 and HIV-2, and the human T-lymphocyte viruses (HTLV-I and HTLV-II), and non-human retroviruses, such as bovine leukosis virus, feline sarcoma and leukemia viruses, simian immunodeficiency viruses (SIV), sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

The antiviral methods of the invention can also be utilized against non-retroviral viruses, including, but not limited to, respiratory syncytial virus (RSV), canine distemper virus, newcastle disease virus, human parainfluenza virus, influenza viruses, measles viruses, Epstein-Barr viruses, hepatitis B viruses and Mason-Pfizer viruses.

The above-recited viruses are enveloped viruses. The antiviral methods of the invention can also be utilized against non-enveloped viruses, including but not limited to picornaviruses such as polio viruses, hepatitis A virus, enterovirus, echoviruses, and coxsackie viruses, papovaviruses such as papilloma virus, parvoviruses, adenoviruses and reoviruses.

Other antifusogenic activities that can be modulated via methods that utilize the peptides of the invention include,

but are not limited to modulation of neurotransmitter exchange via cell fusion, and sperm-egg fusion. Among the intracellular disorders involving coiled-coil interactions that can be ameliorated via methods that utilize the peptides of the invention are disorder involving, for example, bacterial toxins.

The antifusion or antiviral activity of a given core polypeptide or hybrid polypeptide can routinely be ascertained via standard in vitro, ex vivo and animal model assays that, with respect to antiviral activity, can be specific or partially specific for the virus of interest and are well known to those of skill in the art.

The above description relates mainly to antiviral and antifusion-related activities of core and hybrid polypeptides of the invention. The hybrid polypeptides of the invention can also be utilized as part of any method for which administration or use of the core polypeptide alone might be contemplated. Use of hybrid polypeptides as part of such methods is particularly preferable in instances wherein an increase in the pharmacokinetic properties of the core polypeptide is desired. For example, insulin is utilized as part of treatment for certain types of diabetes. A hybrid polypeptide comprising an insulin or insulin fragment as the core polypeptide can, therefore, also be utilized as part of methods for ameliorating symptoms of forms of diabetes for which insulin is used and/or contemplated.

In addition to the above therapeutic methods, the peptides of the invention can still further be utilized as part of prognostic methods for preventing disorders, including, but not limited to disorders involving fusion events, intracellular processes involving coiled-coil peptides and viral infection that involves cell-cell and/or virus-cell fusion. For example, the core and hybrid polypeptides of the invention can be utilized as part of prophylactic methods of preventing viral infection.

The hybrid polypeptides of the invention can still further be utilized as part of diagnostic methods. Such

methods can be either in vivo or in vitro methods. Any diagnostic method that a particular core polypeptide can be utilized can also be performed using a hybrid polypeptide comprising the core polypeptide and a modification or primary amino acid sequence that allows detection of the hybrid polypeptide. Such techniques can reflect an improvement over diagnostic methods in that the increased half life of the hybrid polypeptide relative to the core polypeptide alone can increase the sensitivity of the diagnostic procedure in which it is utilized. Such diagnostic techniques include, but are not limited to imaging methods, e.g., in vivo imaging methods. In a non-limiting example of an imaging method, a structure that binds the core polypeptide of a hybrid polypeptide can be detected via binding to the hybrid polypeptide and imaging (either directly or indirectly) the bound hybrid polypeptide.

5.4. PHARMACEUTICAL FORMULATIONS, DOSAGES AND MODES OF ADMINISTRATION

The peptides of the invention may be administered using techniques well known to those in the art. Preferably, agents are formulated and administered systemically. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences", latest edition, Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, vaginal, lung (e.g., by inhalation), transdermal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few. For intravenous injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer to name a few. In addition, infusion pumps may be used to deliver the peptides of the invention. For transmucosal administration,

penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

In instances wherein intracellular administration of the peptides of the invention or other inhibitory agents is preferred, techniques well known to those of ordinary skill in the art may be utilized. For example, such agents may be encapsulated into liposomes, or microspheres then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are effectively delivered into the cell cytoplasm. Additionally, due to their hydrophobicity, when small molecules are to be administered, direct intracellular administration may be achieved.

Nucleotide sequences encoding the peptides of the invention which are to be intracellularly administered may be expressed in cells of interest, using techniques well known to those of skill in the art. For example, expression vectors derived from viruses such as retroviruses, vaccinia viruses, adeno-associated viruses, herpes viruses, or bovine papilloma viruses, may be used for delivery and expression of such nucleotide sequences into the targeted cell population. Methods for the construction of such vectors and expression constructs are well known. See, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor NY, and Ausubel et al., 1989, Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, NY.

Effective dosages of the peptides of the invention to be administered may be determined through procedures well known to those in the art which address such parameters as biological half-life, bioavailability, and toxicity. In particularly preferred embodiments, an effective hybrid

polypeptide dosage range is determined by one skilled in the art using data from routine *in vitro* and *in vivo* studies well know to those skilled in the art. For example, *in vitro* cell culture assays of antiviral activity, such as the exemplary assays described in Section 7, below, for T1249, will provide data from which one skilled in the art may readily determine the mean inhibitory concentration (IC) of the peptide of the polypeptide necessary to block some amount of viral infectivity (*e.g.*, 50%, IC_{50}; or 90%, IC_{90}). Appropriate doses can then be selected by one skilled in the art using pharmacokinetic data from one or more routine animal models, such as the exemplary pharmacokinetic data described in Section 10, below, for T1249, so that a minimum plasma concentration (C_{min}) of the peptide is obtained which is equal to or exceeds the determined IC value.

Exemplary polypeptide dosages may be as low as 0.1 μg/kg body weight and as high as 10 mg/kg body weight. More preferably an effective dosage range is from 0.1 - 100 μg/kg body weight. Other exemplary dosages for peptides of the invention include 1-5 mg, 1-10 mg, 1-30 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-125 mg, 1-150 mg, 1-200 mg, or 1-250 mg of peptide. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of

circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (e.g., the concentration of the test compound which achieves a half-maximal inhibition of the fusogenic event, such as a half-maximal inhibition of viral infection relative to the amount of the event in the absence of the test compound) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC) or any biological or immunological assay capable of measuring peptide levels.

The hybrid polypeptides of the invention can be administered in a single administration, intermittently, periodically, or continuously. For example, the polypeptides of the invention can be administered in a single administration, such as a single subcutaneous, a single intravenous infusion or a single ingestion. The polypeptides of the invention can also be administered in a plurality of intermittent administrations, including periodic administrations. For example, in certain embodiments the polypeptides of the invention can be administered once a week, once a day, twice a day (*e.g.*, every 12 hours), every six hours, every four hours, every two hours, or every hour. The polypeptides of the invention may also be administered continuously, such as by a continuous subcutaneous or intravenous infusion pump or by means of a subcutaneous or other implant which allows the polypeptides to be continuously absorbed by the patient.

The hybrid polypeptides of the invention can also be administered in combination with at least one other

therapeutic agent. Although not preferred for HIV therapy, administration for other types of therapy (e.g., cancer therapy) can be performed concomitantly or sequentially, including cycling therapy (that is, administration of a first compound for a period of time, followed by administration of a second antiviral compound for a period of time and repeating this sequential administration in order to reduce the development of resistance to one of the therapies).

In the case of viral, e.g., retroviral, infections, an effective amount of a hybrid polypeptide or a pharmaceutically acceptable derivative thereof can be administered in combination with at least one, preferably at least two, other antiviral agents.

Taking HIV infection as an example, such antiviral agents can include, but are not limited to DP-107 (T21), DP-178 (T20), any other core polypeptide depicted in Table 2 derived from HIV-1 or HIV-2, any other hybrid polypeptide whose core polypeptide is, at least in part, derived from HIV-1 or HIV-2, cytokines, e.g., rIFN α, rIFN β, rIFN γ; inhibitors of reverse transcriptase, including nucleoside and non-nucleoside inhibitors, e.g., AZT, 3TC, D4T, ddI, adefovir, abacavir and other dideoxynucleosides or dideoxyfluoronucleosides, or delaviridine mesylate, nevirapine, efavirenz; inhibitors of viral mRNA capping, such as ribavirin; inhibitors of HIV protease, such as ritonavir, nelfinavir mesylate, amprenavir, saquinavir, saquinavir mesylate, indinavir or ABT378, ABT538 or MK639; amphotericin B as a lipid-binding molecule with anti-HIV activity; and castanospermine as an inhibitor of glycoprotein processing.

The hybrid and/or core polypeptides of the invention may, further, be utilized prophylactically for the prevention of disease. Hybrid and/or core polypeptides can act directly to prevent disease or, alternatively, can be used as vaccines, wherein the host raises antibodies against the hybrid polypeptides of the invention, which then serve to neutralize pathogenic organisms including, for example, inhibiting viral, bacterial and parasitic infection.

For all such treatments described above, the exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the oncogenic disorder of interest will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by subcutaneous injection, intravenous injection, by subcutaneous infusion or intravenous infusion, for example by pump. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve

its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions. For oral administration of peptides, techniques such of those utilized by, e.g., Emisphere Technologies well known to those of skill in the art and can routinely be used.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, spray drying, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, emulsions and suspensions of the active compounds may be prepared as appropriate oily injection mixtures. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, liposomes or other substances known in the art for making lipid or lipophilic emulsions. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient,

optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, trehalose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

In instances where an enhancement of the host immune response is desired, the hybrid polypeptides may be formulated with a suitable adjuvant in order to enhance the immunological response. Such adjuvants may include, but are not limited to mineral gels such as aluminum hydroxide;

surface active substances such as lysolecithin, pluronic polyols, polyanions; other peptides; oil emulsions; and potentially useful adjuvants such as BCG and Corynebacterium parvum. Many methods may be used to introduce the vaccine formulations described here. These methods include but are not limited to oral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, and intranasal routes.

6. EXAMPLE: IDENTIFICATION OF CONSENSUS AMINO ACID SEQUENCES THAT COMPRISE ENHANCER PEPTIDE SEQUENCES

The retroviral gp41 protein contains structural domains referred to as the α-helix region located in the C-terminal region of the protein and the leucine zipper region located in the N-terminal region of the protein. Alignment of the enhancer peptide sequence regions contained within gp41 (FIG. 2A and 2B) of gp41 from all currently published isolate sequences of HIV-1, HIV-2 and SIV identified the consensus amino acid sequences shown in FIG. 1.

As described in detail in the Examples presented below, such sequences represent enhancer peptide sequences in that linkage of these peptide sequences to a variety of different core polypeptides enhances the pharmacokinetic properties of the resultant hybrid polypeptides.

7. EXAMPLE: HYBRID POLYPEPTIDES THAT FUNCTION AS POTENT INHIBITORS OF HIV-1 INFECTION

T1249, as depicted in FIG. 13, is a hybrid polypeptide comprising enhancer peptide sequences linked to an HIV core polypeptide. As demonstrated below, the T1249 hybrid polypeptide exhibits enhanced pharmacokinetic properties and potent *in vitro* activity against HIV-1, HIV-2, and SIV isolates, with enhanced activity against HIV-1 clinical isolates in HuPBMC infectivity assays *in vitro* as well as in the HuPBMC SCID mouse model of HIV-1 infection *in vivo*. In the biological assays described below, the activity of the

T1249 is compared to the potent anti-viral T20 polypeptide. The T20 polypeptide, also known as DP-178, is derived from HIV-1 gp41 protein sequence, and is disclosed and claimed in U.S. patent No. 5,464,933.

7.1. MATERIALS AND METHODS

7.1.1. PEPTIDE SYNTHESIS AND PURIFICATION

Peptides were synthesized using Fast Moc chemistry. Generally, unless otherwise noted, the peptides contained amidated carboxyl termini and acetylated amino termini. Purification was carried out by reverse phase HPLC.

T1249 (Ac-WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF-NH_2) is a 39 amino acid peptide (MW = 5036.7) composed entirely of naturally occurring amino acids and is blocked at the amino terminus by an acetyl group and the carboxyl terminus is blocked by an amido group to enhance stability. T1387 is a 23 amino acid peptide lacking enhancer peptide sequences (Ac-TALLEQAQIQQEKNEYELQKLDK-NH_2). Thus, T1387 represents the core polypeptide of the T1249 hybrid polypeptide. T1387 is blocked at its amino- and carboxy- termini in the same manner as T1249.

In particular, T1249 was synthesized using standard solid-phase synthesis techniques. The identity of the principal peak in the HPLC trace was confirmed by mass spectroscopy to be T1249.

T1249 was readily purified by reverse phase chromatography on a 6-inch column packed with a C18, 10 micron, 120A support.

7.1.2. VIRUS

The HIV-1_{LAI} virus (Popovic, M. et al., 1984, Science 224:497-508) was propagated in CEM cells cultured in RPMI 1640 containing 10% fetal calf serum. Supernatant from the infected CEM cells was passed through a 0.2μm filter and the infectious titer estimated in a microinfectivity assay using the AA5 cell line to support virus replication. For this purpose, 20μl of serially diluted virus was added to 20μl CEM

cells at a concentration of 6 x 10^5/ml in a 96-well microtitre plate. Each virus dilution was tested in triplicate. Cells were cultured for seven days by addition of fresh medium every other day. On day 7 post infection, supernatant samples were tested for virus replication as evidenced by reverse transcriptase activity released to the supernatant. The $TCID_{50}$ was calculated according to the Reed and Muench formula (Reed, L.J. <u>et al.</u>, 1938, Am. J. Hyg. <u>27</u>:493-497).

7.1.3. <u>CELL FUSION ASSAY</u>

Approximately 7 x 10^4 Molt-4 cells were incubated with 1 x 10^4 CEM cells chronically infected with the HIV-1_{LAI} virus in 96-well tissue culture plates in a final volume of 100μl culture medium (RPM1 1640 containing 10% heat inactivated FBS, supplemented with 1% L-glutamine and 1% Pen-Strep) as previously described (Matthews, T.J. <u>et al.</u>, 1987, Proc. Natl. Acad. Sci. USA <u>84</u>: 5424-5428). Peptide inhibitors were added in a volume of 10μl and the cell mixtures were incubated for 24 hr. at 37°C in 5% CO_2. At that time, multinucleated giant cells (syncytia, five cell widths or larger) were counted by microscopic examination at 10x and 40x magnification which allowed visualization of the entire well in a single field. Treated cells were compared to infected, untreated controls and results expressed as percent inhibition of infected controls.

7.1.4. <u>MAGI-CCR-5 INFECTIVITY ASSAYS</u>

Approximately 1 x 10^6 Magi-CCR-5 cells (obtained through the NIH AIDS Research and Reference Reagent Program, Division of AIDS, NIAID; Chackerian, B. et al., 1997, J. Virol. <u>71</u>: 3932-3939) were seeded into a 48-well tissue culture plate (approximately 2 x 10^4 cells/well in a volume of 300 μl/well selective growth medium consisting of DMEM supplemented with 10% heat inactivated FBS, 1% L-glutamine, 1% Pen/Strep, Hygromycin B, Geneticin, and Puromycin) and allowed to attach overnight at 37°C, 5% CO_2. Cell confluency was approximately

30% by the following day. Seeding medium was removed and diluted peptide inhibitor added in volumes of 50 μl/well (media only in untreated controls), followed by 100 μl/well of diluted virus (desired input virus titre of 100 - 200 pfu/well). Finally, 250 μl of selective growth medium was added to each well and the plate incubated for 2 days at 37°C, 5% CO_2. Fixing and staining were done according to the protocol provided by NIAID with the MAGI-CCR5 cells. Briefly, medium was removed from the plate and 500 μl of fixative added to each well. Plates were allowed to fix for 5 minutes at room temp. Fixative was removed, each well washed twice with DPBS, and 200 μl of staining solution added to each well. The plate was then incubated at 37°C, 5% CO_2, for 50 minutes, staining solution removed, and each well washed twice with DPBS. The plate was allowed to air dry before blue cells were counted by microscopic, enumerating the entire well. Treated wells were compared to infected, untreated controls and results expressed as percent inhibition of infected controls.

7.1.5. REVERSE TRANSCRIPTASE ASSAY

The micro-reverse transcriptase (RT) assay was adapted from Goff et al. (Goff, S. et al., 1981, J. Virol. 38: 239-248) and Willey et al. (Willey, R. et al., 1988, J. Virol. 62: 139-147). Supernatants from virus/cell cultures were adjusted to 1% Triton-X100. 10 μl of each supernatant/Triton X-100 sample were added to 50 ul of RT cocktail (75 mM KCl, 2 mM Clevelands reagent, 5 mM $MgCl_2$, 5 μg/ml poly A, 0.25 units/ml oligo dT, 0.05% NP40, 50 mM Tris-HCl, pH 7.8, 0.5 μM non-radioactive dTTP, and 10 cCi/ml ^{32}P-dTTP) in a 96-well U-bottom microtitre plate and incubated at 37°C for 90 min. After incubation, 40 μl of reaction mixture from each well was transferred to a Schleicher and Schuell (S+S) dot blot apparatus, under partial vacuum, containing a gridded 96-well filter-mat (Wallac catalog #1450-423) and filter backing saturated with 2x SSC buffer (0.3M NaCl and 0.003M sodium citrate). Each well was washed 4 times with at least 200 μl

2x SSC using full vacuum. Minifold was disassembled and gridded filter paper removed and washed 3 times with 2x SSC. Finally, the filter membrane was drained on absorbent paper, allowed to air dry, and sealed in heat sealable bags. Samples were placed in a phosphorscreen cassette and an erased (at least 8 min) phosphorscreen applied and closed. Exposure was for 16 hr. Pixel Index Values (PIV), generated in volume reporting format retrieved from phosphorimaging (Molecular Dynamics Phosphorimager) blots, were used to determine the affected or inhibited fraction (Fa) for all doses of inhibitor(s) when compared to untreated, infected controls (analyzed by ImageQuant volume report, corrected for background).

7.1.6. HUMAN PBMC INFECTIVITY/NEUTRALIZATION ASSAY

The prototypic assay used cell lines where the primary isolate assay utilizes PBMC, obtained through Interstate Blood Bank, activated for 2-3 days with a combination of OKT3 (0.5 μg/ml) and CD28 antibodies (0.1 μg/ml). The target cells were banded on lymphocyte separation medium (LSM), washed, and frozen. Cells were thawed as required and activated as indicated above a minimum of 2-3 days prior to assay. In this 96-well format assay, cells were at a concentration of 2 x 10^6/ml in 5% IL-2 medium and a final volume of 100 μl. Peptide stock solutions were made in DPBS (1 mg/ml). Peptide dilutions were performed in 20% FBS RPM1 1640/5% IL-2 complete medium.

7.1.7. IN VIVO HU-PBMC SCID MODEL OF HIV-1 INFECTION

Female SCID mice (5-7 weeks old) received 5-10x10^7 adult human PBMC injected intraperitoneally. Two weeks after reconstitution, mice were infected IP on day 0 with 10^3 $TCID_{50}$ HIV-1 9320 (AZT-sensitive isolate A018). Treatment with peptides was IP, bid, beginning day -1 and continuing through day 6. The extent of infection in blood cells, splenocytes,

lymph nodes, and peritoneal cells was assayed by quantitative co-culture with human PBMC blasts weekly for three consecutive weeks following animal exsanguinations and tissue harvest (day 7, approximately 12-18 hours following the last drug treatment). Co-culture supernatants were evaluated for HIV-1 p24 antigen production as a measure of virus infection (Immunotek Coulter kits and protocol).

7.1.8. RAT PHARMACOKINETIC STUDIES

250-300 g male CD rats, double jugular catheter, obtained from Charles River Laboratories were used. Peptides were injected in one jugular catheter in a volume of 200 μl of peptide solution (approximately 3.75 mg/ml), dosing solution concentration was determined using the Edelhoch method, (Edelhoch, 1967, Biochemistry 6:1948-1954) method and adjusted based on animal weight such that each animal received a dose of 2.5 mg/kg). Approximately 250-300 μl of blood was removed at predetermined time intervals (0, 15, 30 min and 1, 2, 4, 6, and 8 hours) and added to EDTA capiject tubes. Plasma was removed from pelleted cells upon centrifugation and either frozen or immediately processed for fluorescence HPLC analysis.

7.1.9. FLUORESCENCE HPLC ANALYSIS OF PLASMA SAMPLES

100 μl of sample plasma was added to 900 μl of precipitation buffer (acetonitrile, 1.0% TFA, detergent) resulting in precipitation of the majority of plasma proteins. Following centrifugation at 10,000 rpm for 10 min, 400 μl of the supernatant was removed and added to 600 μl of HPLC grade water. Serial dilutions were performed as dictated by concentration of peptide present in each sample in dilution buffer comprised of 40% precipitation buffer and 60% HPLC water. In addition to sample dilutions, serial dilutions of dosing solution were performed in buffer as well as in plasma and used to generate a standard curve relating peak area to known concentration of peptide. This curve was

then used to calculate concentration of peptide in plasma taking into account all dilutions performed and quantity injected onto column.

7.1.10. XTT PROTOCOL

In order to measure cytotoxic/cytostatic effects of peptides, XTT assays (Weislow, O.S. et al., 1989, J. Natl. Cancer Inst. 81:577-586) were performed in the presence of varying concentrations of peptide in order to effectively establish a selective index (SI). A TC_{50} was determined in this assay by incubating cells in the presence and absence of serially diluted peptide followed by the addition of XTT. In surviving/metabolizing cells XTT is reduced to a soluble brown dye, XTT-formazan. Absorbance is read and comparisons made between readings in the presence and absence of peptide to determine a TC_{50} utilizing the Karber method (see. e.g., Lennette, E.H. et al., eds., 1969, "Diagnostic Procedures for Viral and Rickettsial Infections," American Public Health Association, Inc., fourth ed., pp. 47-52). Molt 4, CEM (80,000 cells/well) and a combination of the two cell types (70,000 and 10,000 respectively) were plated and incubated with serially diluted peptide for 24 hours in a total volume of 100 µl. Following incubation, 25 µl of XTT working stock (1 mg/ml XTT, 250 µM PMS in complete medium containing 5% DMSO) was added to each well and the plates incubated at 37°C. Color development was read and results used to express values generated from peptide containing wells as a percentage of the untreated control wells.

7.2. RESULTS

7.2.1. ANTIVIRAL ACTIVITY - FUSION ASSAYS

T1249 was directly compared to T20 in virus mediated cell-cell fusion assays conducted using chronically infected CEM cells mixed with uninfected Molt-4 cells, as shown in Table 3, below. T1249 fusion inhibition against lab isolates such as IIIb, MN, and RF is comparable to T20, and displays

an approximately 2.5-5-fold improvement over T20. T1249 was also more active (3-28 fold improvement) than T20 against several syncytia-inducing clinical isolates, including an AZT resistant isolate (G691-2), a pre-AZT treatment isolate (G762-3), and 9320 (isolate used in HuPBMC-SCID studies). Most notably, T1249 was over 800-fold more potent than T20 against HIV-2 NIHZ.

TABLE 3

Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml)	n	Fold Difference
HIV-1 IIIb	2.5	9	1.0	9	2.5
HIV-1 G691-2 (AZT-R)	406.0	1	16.0	1	25
HIV-1 G762-3 (Pre-AZT)	340.1	1	12.2	1	28
HIV-1 MN	20.0	7	3.1	7	6
HIV-1 RF	6.1	7	2.1	7	3
HIV-1 9320	118.4	1	34.5	1	3
HIV-2 NIHZ	3610.0	>10	4.3	2	840

7.2.2. ANTIVIRAL ACTIVITY - Magi-CCR-5 INFECTIVITY ASSAYS

Magi-CCR-5 infectivity assays allow direct comparisons to be made of syncytia and non-syncytia inducing virus isolates, as well as comparisons between laboratory and clinical isolates. The assay is also a direct measure of virus infection (TAT expression following infection, transactivating an LTR driven beta-galactosidase production), as opposed to commonly used indirect measures of infectivity such as p24 antigen or reverse transcriptase production. Magi-CCR-5 infectivity assays (see Table 4 below) reveal that T1249 is consistently more effective than T20 against all isolates tested, in terms of both EC_{50} and Vn/Vo = 0.1 inhibition calculations. T1249 shows considerable improvement in potency against the clinical isolate HIV-1

301714 (>25-fold), which is one of the least sensitive isolates to T20. In addition, T1249 is at least 100-fold more potent than T20 against the SIV isolate B670. These data, along with fusion data suggest that T1249 is a potent peptide inhibitor of HIV-1, HIV-2, and SIV.

TABLE 4

	T20		T1249			
Virus Isolate	EC-50	Vn/Vo=0.1	EC-50	Vn/Vo=0.1	EC-50 Fold Difference	Vn/Vo=0.1 Fold Difference
HIV-1 IIIB	42	80	8	10	5	8
HIV-1 9320	11	50	1	6	11	8
HIV-1 301714 (subtype B, NSI)	1065	4000	43	105	25	38
HIV-1 G691-2 (AZT-R)	13	200	0.3	20	43	10
HIV-1 pNL4-3	166	210	1	13	166	16
SIV-B670	2313	>10000	21	100	110	>100

7.2.3. <u>ANTIVIRAL ACTIVITY - HuPBMC INFECTIVITY ASSAYS</u>

T1249 was directly compared to T20 in HuPBMC infectivity assays (Table 5, below), which represent a recognized surrogate *in vitro* system to predict plasma drug concentrations required for viral inhibition *in vivo*. These comparisons revealed that T1249 is more potent against all HIV-1 isolates tested to date, with all Vn/Vo = 0.1 (dose required to reduce virus titer by one log) values being reduced to sub-microgram concentrations. Many of the least

sensitive clinical isolates to T20 exhibited 10-fold or greater sensitivity to T1249. It is noteworthy that HIV-1 9320, the isolate used in the HuPBMC SCID mouse model of infection, is 46-fold less sensitive to T20 than to T1249, indicating a very good correlation with the *in vivo* results.

TABLE 5

	T20	T1249	
Virus Isolate (HIV-1)	Vn/Vo = 0.1 (ng/ml)	Vn/Vo = 0.1 (ng/ml)	Fold Difference
IIIB	250	80	3
9320	6000	130	46
301714 (subtype B, NSI)	8000	700	11
302056 (subtype B, NSI)	800	90	9
301593 (subtype B, SI)	3500	200	18
302077 (subtype A)	3300	230	14
302143 (SI)	1600	220	7
G691-2 (AZT-R)	1300	400	3

7.2.4. ANTIVIRAL ACTIVITY - T20 RESISTANT LAB ISOLATES

T1249 was directly compared to T20 in virus mediated cell-cell fusion assays conducted using chronically infected CEM cells mixed with uninfected Molt-4 cells (Table 6, below). T1249 was nearly 200-fold more potent than T20 against a T20-resistant isolate.

TABLE 6

Virus Isolate	T20 (ng/ml)	n	T1249 (ng/ml)	n	Fold Difference
HIV-1 pNL4-3 SM (T20 Resistant)	405.3	3	2.1	3	193

In Magi-CCR-5 assays (see Table 7, below), T1249 is as much as 50,000-fold more potent than T20 against T20-resistant isolates such as pNL4-3 SM and pNL4-3 STM (Rimsky, L. and Matthews, T., 1998, J. Virol. 72:986-993).

TABLE 7

	T20		T1249			
Virus Isolate (HIV-1)	EC-50	Vn/Vo = 0.1	EC-50	Vn/Vo=0.1	EC-50 Fold Difference	Vn/Vo=0.1 Fold Difference
pNL4-3	166	210	1	13	166	16
pNL4-3 SM (T20-R)	90	900	4	11	23	82
pNL4-3 SM (T20-R) Duke	410	2600	4	11	103	236
pNL4-3 STM (T20/T649-R)	>50 000	>5000 0	1	13	>50000	>3846

T1249 was directly compared to T20 in HuPBMC infectivity assays (see Table 8, below), evaluating differences in potency against a resistant isolate. T1249 is greater than 250-fold more potent than T20 against the resistant isolate pNL4-3 SM.

TABLE 8

	T20	T1249	
Virus Isolate (HIV-1)	Vn/Vo = 0.1 (ng/ml)	Vn/Vo = 0.1 (ng/ml)	Fold Difference
pNL4-3	3500	30	117
pNL4-3 SM (T20-R)	>10000	40	>250

7.2.5. ANTIVIRAL ACTIVITY - *IN VIVO* SCID-HuPBMC MODEL

In vivo antiviral activity of T1249 was directly compared to T20 activity in the HuPBMC-SCID mouse model of HIV-1 9320 infection (FIG. 3). Two weeks after reconstitution with HuPBMCs, mice were infected IP on day 0 with 10^3 $TCID_{50}$ HIV-1 9320 passed in PBMCs (AZT-sensitive isolate A018). Treatment with peptides was IP, bid, for total daily doses of 67 mg/kg (T20), 20 mg/kg (T1249), 6.7 mg/kg (T1249), 2.0 mg/kg (T1249), and 0.67 mg/kg (T1249), for 8 days beginning on day -1. The extent of infection in blood cells, splenocytes, lymph nodes, and peritoneal cells was assayed by quantitative co-culture with human PBMC blasts weekly for three consecutive weeks following animal exsanguinations and tissue harvest (day 7, approx. 12 to 18 hours following last drug treatment). Co-culture supernatants were evaluated for HIV-1 p24 antigen production as a measure of virus infection. Infectious virus was not detectable in the blood or lymph tissues of the T20-treated animals, although, virus was detected in the peritoneal washes and spleen preparation. All compartments were negative for infectious virus at the 6.7 mg/kg dose of T1249, indicating at least a 10-fold improvement over T20 treatment. At the 2.0 mg/kg dose of T1249, both the lymph and the spleen were completely free of detectable infectious virus, with a 2 $\log_{10}$ reduction in virus titer in the peritoneal wash and a 1 $\log_{10}$ reduction in virus titer in the blood, compared to infected controls. At the lowest dose of T1249, 0.67 mg/kg, the peritoneal washes and blood were equivalent to infected control; however, at least a 1 $\log_{10}$ drop in infectious virus titer was observed in both the lymph and the spleen tissues. Overall, the results indicate that T1249 is between 30 and 100-fold more potent against HIV-1 9320, *in vivo*, under these conditions.

7.2.6. PHARMACOKINETIC STUDIES - RAT

Cannulated rats were used to further define the pharmacokinetic profile of T1249. Male CD rats, 250-300 g, were dosed IV through a jugular catheter with T1249 and T20 (FIGS. 4A-5). The resulting plasma samples were evaluated using fluorescence HPLC to estimate peptide quantities in extracted plasma. The beta-phase half-life and total AUC of T1249 was nearly three times greater than T20 (FIG. 5).

7.2.7. CYTOTOXICITY

No overt evidence of T1249 cytotoxicity has been observed *in vitro*, as demonstrated in FIG. 6.

In addition, T1249 is not acutely toxic (death within 24 hours) at 167 mg/kg (highest dose tested) given IV through jugular cannula (0.3 ml over 2-3 min).

7.2.8. DIRECT BINDING TO gp41 CONSTRUCT M41 Δ 178

T1249 was radiolabelled with ^{125}I and HPLC- purified to maximum specific activity. T20 was iodinated in the same manner. Saturation binding of to M41Δ178 (a truncated gp41 ectodomain fusion protein lacking the T20 amino acid sequence) immobilized on microtitre plates at 0.5 mg/μl is shown in FIG.7. Nonspecific binding was defined as binding of the radioligand in the presence of 1 μM unlabeled peptide. Specific binding was the difference between total and nonspecific binding. The results demonstrate that ^{125}I-T1249 and ^{125}I-T20 have similar binding affinities of 1-2 nM. Linear inverse Scatchard plots suggests that each ligand binds to a homogeneous class of sites.

The kinetics of ^{125}I-T1249 and ^{125}I-T20 binding was determined on scintillating microtitre plates coated with 0.5 μg/ml M41Δ178. The time course for association and dissociation is shown in FIG.8. Dissociation of bound radioligand was measured following the addition of unlabeled peptide to a final concentration of 10 μM in one-tenth of the total assay volume. Initial on- and off-rates for ^{125}I-T1249

were significantly slower than those of ^{125}I-T20. Dissociation patterns for both radioligands were unchanged when dissociation was initiated with the other unlabeled peptide (*i.e.*, ^{125}I-T1249 with T20).

To further demonstrate that both ligands compete for the same target site, unlabeled T1249 and T20 were titrated in the presence of a single concentration of either ^{125}I-T1249 or ^{125}I-T20. Ligand was added just after the unlabeled peptide to start the incubation. The competition curves shown in FIG.9 suggest that although both ligands have similar affinities, a higher concentration of either unlabeled T20 or T1249 is required to fully compete for bound ^{125}I-T1249.

7.2.9. DIRECT BINDING TO THE HR1 REGION OF GP41

Circular dichroism (CD) spectroscopy was used to measure the secondary structure of T1249 in solution (phosphate-buffered saline, pH 7) alone and in combination with a 45-residue peptide (T1346) from the HR1 (heptad repeat 1) binding region of gp 41. FIG. 14A illustrates the CD spectrum of T1249 alone in solution (10 μM, 1ºC). The spectrum is typical of peptides which adopt an alpha-helical structure. In particular, deconvolution of this spectrum using single value decomposition with a basis set of 33 protein spectra predicts the helix content of T1249 (alone in solution) to be 50%. FIG. 14B illustrates a representative CD spectrum of T1249 mixed with T1346. The closed squares (■) represent a theoretical CD spectrum predicted for a "non-interaction model" wherein the peptides are hypothesized to not interact in solution. The actual experimental spectrum (●) differs markedly from this theoretical "non-interaction model" spectrum, demonstrating that the two peptides do, indeed, interact, producing a measurable structural change which is observed in the CD spectrum.

7.2.10. PROTEASE PROTECTION OF THE T1249 BINDING REGION WITHIN GP41

The susceptibility of the chimeric protein M41Δ178, described in Section 7.2.8 above, to proteinase-K digestion was determined and analyzed by polyacrylamide gel electrophoresis. The results are illustrated in FIG. 15.

When either M41Δ178 (untreated; FIG 15, lane 2) or T1249 (untreated; FIG. 15, lane 4) are incubated individually with proteinase K (FIG. 15, lanes 3 and 5, respectively), both are digested. However, when T1249 is incubated with M41Δ178 prior to addition of proteinase-K (FIG. 15, lane 7), a protected HR-1 fragment of approximately 6500 Daltons results. Sequencing of the protected fragment demonstrates that it corresponds to a region of primary sequence located within the ectodomain of gp41. The protected fragment encompasses the soluble HR1 peptide (T1346) used in the CD studies described in Section 7.2.9 above, and further contains an additional seven amino acid residues located on the amino terminus. This protection can be attributed to the binding of T1249 to a specific sequence of gp41 which is contained in the M41Δ178 construct.

8. EXAMPLE: RESPIRATORY SYNCYTIAL VIRUS HYBRID POLYPEPTIDES

The following example describes respiratory syncytial virus (RSV) hybrid polypeptides with enhanced pharmacokinetic properties. In addition, results are presented, below, which demonstrate that the RSV hybrid polypeptides represent potent inhibitors of RSV infection.

8.1. MATERIALS AND METHODS

8.1.1. PEPTIDE-SYNTHESIS AND PURIFICATION

RSV polypeptides were synthesized using standard Fast Moc chemistry. Generally, unless otherwise noted, the peptides contained amidated carboxyl termini and acetylated amino termini. Purification was carried out by reverse phase HPLC.

8.1.2. RESPIRATORY SYNCYTIAL VIRUS PLAQUE REDUCTION ASSAY

All necessary dilutions of peptides were performed in clean, sterile 96-well TC plate. A total of eleven dilutions for each peptide and one control well containing no peptide were assembled. The final concentration range of peptide started at 50μg/ml or 100μg/ml, with a total of eleven two-fold dilutions. The RSV was prepared at a concentration of 100PFU/well in 100μl 3% EMEM, as determined by a known titer of RSV. The virus is then added to all of the wells.

The media was removed from one sub-confluent 96-well plate of Hep2 cells. The material from the dilution plate was transferred onto the cell plates starting with row 1 and then transferring row 12, row 11, etc. until all rows were transferred. Plates were placed back into the incubator for 48 hours.

The cells were checked to ensure that syncytia were present in the control wells. Media was removed and approximately 50 μls of 0.25% Crystal Violet in methanol was added to each well. The wells were rinsed immediately in water to remove excess stain and allowed to dry. Using a dissecting microscope, the number of syncytia in each well was counted.

8.2. RESULTS

Pharmacokinetic studies with the RSV hybrid peptides T1301 (Ac-WQEWDEYDASISQVNEKINQALAYIREADELWA WF-NH_2) and T1302 (Ac-WQAWDEYDASISQVNEKINQALAYIREADELW AWF-NH_2) containing enhancer peptide sequences demonstrated a greatly enhanced half-life relative to core peptide T786 (Ac-VYPSDEYDASISQVNEEINQALAYIRKADELLENV-NH_2), as demonstrated in FIG. 10A-10B. Hybrid polypeptides T1301, T1302 and T1303 (Ac-WQAWDEYDASISDVNEKINQALAYIREADELWEWF-NH_2) also showed a greatly enhanced half-size relative to core peptide T1476 (Ac-DEYDASISQVNEKINQALAYIREADEL-NH_2).

RSV hybrid polypeptides T1301, T1302 and T1303, as well as polypeptide T786 and T1293, were tested for their ability

to inhibit RSV plaque formation of HEp2 cells. As indicated in FIGS. 11A and 11B, both the tested hybrid RSV polypeptides, as well as the T786 core polypeptide were able to inhibit RSV infection. Surprisingly, the T1293 hybrid polypeptide was also revealed to be a potent anti-RSV compound (FIG. 13).

9. EXAMPLE: LUTEINIZING HORMONE HYBRID POLYPEPTIDES

The example presented herein describes luteinizing hormone (LH) hybrid proteins with enhanced pharmacokinetic properties. The following LH hybrid peptides were synthesized and purified using the methods described above: core peptide T1323 (Ac-QHWSYGLRPG-NH_2) and hybrid polypeptide T1324 (Ac-WQEWEQKIQHWSYGLRPGWASLWEWF-NH_2) which comprises the core polypeptide T1323 amino acid sequence coupled with enhancer peptides at its amino- and carboxy-termini. As demonstrated in FIG. 12A and 12B, the T1324 hybrid peptide exhibited a significantly increased half-life when compared to the T1323 core peptide which lacks the enhancer peptide sequences.

10. EXAMPLE: PHARMACOLOGY OF HYBRID POLYPEPTIDE T1249

T1249, depicted in FIG. 13, is a hybrid polypeptide comprising enhancer peptide sequences linked to a core polypeptide derived from a mix of viral sequences. As demonstrated in the Example presented in Section 7 above, the T1249 hybrid polypeptide exhibits enhanced pharmacokinetic properties and potent *in vitro* as well as *in vivo* activity against HIV-1. In the example presented below, the pharmacological properties of T1249 in both rodent and primate animal models are further described.

10.1. MATERIALS AND METHODS

10.1.1. SINGLE-DOSE ADMINISTRATION TO RODENTS

T1249 was administered to Sprague-Dawley albino rats in a single dose administered by continuous subcutaneous infusion (SCI), subcutaneous (SC) injection or intravenous (IV) injection. Each treatment group consisted of nine rats per sex per group. The groups received sterile preparations of T1249 bulk drug substance at a dose of 0.5, 2.0, or 6.5 mg/kg by CSI. One group received 50mM carbonate-bicarbonate, pH 8.5, administered as a control. The peptides were given for 12 hours via a polyvinyl chloride/polyethylene catheter surgically implanted subcutaneously in the nape of the neck. Two groups received a single dose of T1249 at a dose of 1.2 or 1.5 mg/kg by subcutaneous injection into the intrascapular region. Two groups received a single dose of T1249 at a dose of 1.5 or 5 mg/kg via intravenous injection. The actual milligram amount of T1249 was calculated using the peptide content that was determined for the batch administrated.

Endpoints for analysis included cageside observations (twice daily for mortality and moribundity), clinical observations, clinical laboratory parameters, body weight and necropsy. Blood samples were obtained by a sparse sampling technique over a 12 hour time period from three rats per sex per group at each of the following times: 0.5, 1, 2, 4, 6, 8, 19, and 12 hours after dose administration. Sample analysis was performed using a PcAb ECLIA assay (Blackburn, G. et al., 1991, Clin. Chem. 37:1534-1539; Deaver, D., 1995, Nature 377:758).

For plasma and lymphatic pharmacokinetic analysis of T1249 in rats, T1249 was prepared as a sterile solution in bicarbonate buffer and administered as a single dose, bolus intravenous injection into the lateral tail vain at a dose of 20 mg/kg. Blood was collected from the animal from an in-dwelling jugular catheter. Samples were collected immediately after dosing and at 5, 15, and 30 minutes, and 1, 2, 4, and 6 hours after drug administration. For the

analysis of lymphatic fluids, samples were taken immediately before dosing and every 20 minutes for the first six hours after dosing. Lymphatic fluid was collected from a catheter placed directly into the thoracic lymphacic duct as previously described (Kirkpatrick and Silver, 1970, *The Journal of Surgical Research 10*:147-158). The concentrations of T1249 in plasma and lymphatic fluid were determined using a standard T1249 Competitive ELISA assay (Hamilton, G. 1991, p. 139, in "Immunochemistry of Solid-Phase Immunoassay,", Butler, J., ed., CRC Press, Boston).

10.1.2. SINGLE-DOSE ADMINISTRATION TO PRIMATES

Sterile preparations of T1249 bulk drug substance were administered to cynomolgus monkeys in single doses administered by subcutaneous (SC), intramuscular (IM) or intravenous (IV) injection. In a sequential crossover design, one group of animals consisting of two per sex received a single bolus dose of T1249 by IV (0.8 mg/kg), IM (0.8 mg/kg) or SC (0.4, 0.8, and 1.6 mg/kg) injection. A washout period of at least three days separated each dosing day. Lyophilized T1249 was reconstituted in sterile phosphate buffered saline pH 7.4 immediately prior to dosing. The actual milligram amount of test article was calculated using the peptide content that was determined for the batch administered.

Endpoints for analysis included cageside observations, physical examinations and body weight. For the IV phase of the study, blood samples were collected into heparinized tubes at the following time points: immediately after dosing, 0.25, 0.5, 1.5, 3, 6, 12, and 24 hours after dosing. For the IM and SC phases of the study blood samples were collected in heparinized tubes from each animal at the following time points: 0.5, 1, 2, 3, 6, 12, and 24 hours after dosing. Plasma samples were prepared within one hour of collection and flash frozen in liquid nitrogen. Samples analysis was performed using a PcAb ECLIA assay (Blackburn,

G. et al., 1991, Clin. Chem. 37:1534-1539; Deaver, D., 1995, Nature 377:758).

10.1.3. BRIDGING PHARMACOKINETIC STUDY

Six male cynomolgus monkeys were randomly assigned to three groups consisting of two animals per group. All doses of T1249 were given by bolus subcutaneous injection. The study was divided into two sessions. In Session 1, animals in groups 1, 2 and 3 received a sterile preparation of T1249 bulk drug substance (i.e., bulk +1249 dissolved in carbonate-bicarbonate, pH 8.5) twice daily for four consecutive days (Study Days 1-4) at doses of 0.2, 0.6 and 2.0 mg/kg/dose, respectively. A ten day washout period separated Session 1 and Session 2. In Session 2, animals in groups 1, 2, and 3 received a sterile preparation of T1249 drug product (i.e., in aqueous solution, pH 6.5, plus mannitol) twice daily for four consecutive days (Study Days 15-18) at doses of 0.2, 0.6 and 2.0 mg/kg/dose, respectively.

Blood samples for pharmacokinetic analyses were collected on Study Days 1 and 15 to assess single-dose pharmacokinetic parameters, and on Study Days 4 and 18 to assess steady-state plasma pharmacokinetic parameters. Samples were collected at the following times: immediately pre-dose, and 0.5, 1.5, 3.0, 4.0, 6.0, 8.0 and 12.0 hours post-dose. Animals were monitored during Sessions 1 and 2 for clinical signs and changes in body weight.

10.2. RESULTS

10.2.1. PHARMACOKINETICS OF T1249 ADMINISTERED TO RATS

Rat models were used to perform an initial assessment of plasma pharmacokinetics and distribution of T1249. For animals in all dose groups, there were no changes in body weight, physical observations, hematology and clinical chemistry parameters or macroscopic pathology observations related to the administration of T1249.

Rats that received T1249 by CSI achieved steady-state plasma peptide concentrations approximately four hours after administration. Both the steady-state concentration in plasma (Cp_{ss}) and calculated area under the plasma concentration versus time curve (AUC) were directly proportional to the administered dose, indicating that T1249 displays linear pharmacokinetics within the tested dose range of 0.5 to 6.5 mg/kg. Both the calculated pharmacokinetic parameters and the plasma concentration versus time curves for the CSI route of administration are presented in Table 9 and in FIG. 16A, respectively.

TABLE 9

	Dose Groups		
Parameter	0.5 mg/kg	2.0 mg/kg	6.5 mg/kg
Cp_{ss} (μg/ml)	0.80	2.80	10.9
$AUC_{(0-12h)}$ (μg•h/ml)	7.99	25.9	120

Administration of T1249 by bolus IV injection resulted in linear dose-dependent pharmacokinetics within the doses tested. In contrast, exposure to T1249 by SC injection was not dose-dependent within the dose range studied. The calculated pharmacokinetic parameters and plasma concentration versus time curves for both SC and IV administration of T1249 are shown in Table 10 and FIG. 16B respectively.

TABLE 10

	Dose Groups/Administration			
	(SC)		(IV)	
Parameter	1.2 mg/kg	15 mg/kg	1.5 mg/kg	5.0 mg/kg
$t_{1/2,\ terminal}$ (hours)	2.02	2.00	2.46	1.86

t_{max} (hours)	1.09	1.88	-	-
C_{max} (μg/ml)	6.37	21.5	15.7	46.3
$AUC_{(0-12h)}$ (μg•h/ml)	27.0	107	45.6	118
$AUC_{(0-\infty)}$ (μg•h/ml)	27.6	110	47.1	120

The bioavailability of T1249 administered to rats by subcutaneously was determined relative to IV administration. The results are shown in Table 11 below. At low dose (1.2 mg/kg) T1249 exhibited a relative bioavailability (F_R) of 73% for subcutaneous administration. Relative bioavailability was 30% when high-dose (15 mg/kg) administration of T1249 concentration was greater than the concentration that inhibits 90% (IC_{90}) of HIV infectivity for the full 12 hours of the study at all doses examined.

TABLE 11

Route	Dose (mg/kg)	$AUC_{(0-\infty)}$ (μg•h/ml)	Normalized $AUC_{(0-\infty)}$ (μg•h/ml)	F_R (%)
Low Dose				
SC	1.2	27.6	34.5[a]	73
IV	1.5	47.1	-	-
High Dose				
SC	15	110	36.5[b]	30
IV	5	120	-	-

[a] Normalized from a 1.2 mg/kg dose to a 1.5 mg/kg dose by multiplying $AUC_{(0-\infty)}$ by 1.25.
[b] Normalized from a 15 mg/kg dose to a 5 mg/kg dose by dividing $AUC_{(0-\infty)}$ by 3.

The kinetic data for both plasma and lymph concentrations of T1249 are illustrated in FIG. 16C and tabulated below in Table 12. T1249 rapidly penetrated into the lymphatic system and equilibrated with the plasma reservoir of drug within approximately one hour after

administration. Following equilibration between the two compartments, plasma and lymph levels of drug were comparable out to three hours post-dosing in four out of five animals. One animal had consistently lower concentrations of T1249 in the lymph than the other animals, however this animal's lymph elimination profile was indistinguishable from other members of the group. Comparison of the elimination phase half-life (t1/2) for plasma and lymph suggest that the transit of T1249 between these two compartments is a diffusion-controlled process. After three hours, there appeared to be a second, more rapid elimination phase from the lymphatic system. This difference could be mechanism-based (*e.g.*, due to redistribution or accelerated peptide degradation in the lymph) or due to other factors. The concentration of T1249 in lymphatic fluid six hours post-injection is greater than the IC_{90} for viral infectivity for common laboratory strains and for primary clinical isolates of HIV-1.

The extent of penetration of T1249 into cerebrospinal fluid (CSF) was also assessed. T1249 concentrations were below the limit of detection (LOD; 2.0 ng T1249/ml CSF) at all measurable time points, indicating that T1249 does not penetrate the central nervous system after a single dose administration.

TABLE 12

	T1249	
Parameter	**Plasma**	**Lymph**
$t_{1/2}$, elimination (hours)	2.6±0.41	1.3±0.27
C_{max} (μg/ml)	291	133[a]/155[b]
$AUC_{(0-6h)}$ (μg•h/ml)	506	348[a]/411[b]
$AUC_{(0-\infty)}$ (μg•h/ml)	598	390[a]/449[b]
Cl (ml/h)	7.8	11.5

[a] Calculated averages include one animal (Rat #1) that exhibited significantly lower lymph concentrations but a similar kinetic profile by comparison to the other animals in the group.

[b] Calculated averages that exclude Rat #1.

10.2.2. PHARMACOKINETICS OF T1249 ADMINISTERED TO PRIMATES

Primate models were used to evaluate the relationship between dose level and various pharmacokinetic parameters associated with the parenteral administration of T1249. Plasma concentrations greater than 6.0 μg/ml of T1249 were achieved by all routes of administration and quantifiable levels (*i.e.*, levels greater than 0.5 μg/ml) were detected at 24 hours after SC and IV administration. The elimination $t_{1/2}$ was comparable for all routes of administration (5.4 hours, 4.8 hours and 5.6 hours for IV, SC and IM administration, respectively). Plasma concentrations of T1249 that exceed the IC_{90} values for laboratory strains and clinical isolates of HIV-1 were observed at all measured time points throughout the 24 hour sampling period.

A comparison of the data obtained for the parenteral administration of 0.8 mg/kg T1249 via all routes of administration (SC, IV, and IM) is presented in FIG. 17A. FIG. 15B illustrates a comparison of the data obtained from SC injection at three different dose levels of T1249 (0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg). The insert in FIG. 17B contains a plot of the calculated AUC versus administered dose.

T1249 displays linear pharmacokinetics in cynomolgus monkeys following SC administration within the range of administered doses, indicating that saturation of the clearance mechanism or mechanisms has not occurred within this range. A summary of the pharmacokinetic data following parenteral administration of T1249 to cynomolgus monkeys is provided in Table 13, below. A comparison of the plasma AUC values indicates that, relative to intravenous administration, the bioavailability of T1249 is approximately

64% when given by intramuscular injection and 92% when given by subcutaneous injection.

Table 13

Parameter	Administration Route (Dose Level, mg/kg)				
	SC (0.4)	SC (0.8)	SC (1.6)	IM (0.8)	IV (0.8)
$t_{1/2,\ terminal}$ (h)	6.23±0.52	4.83±0.48	5.55±0.92	5.57±0.24	5.35±0.95
t_{max} (h)	3.97±1.18	4.58±1.45	4.72±1.81	2.32±0.43	-
C_{max} (μg/ml)	3.17±0.09	6.85±1.01	13.3±2.55	6.37±1.69	26.7±0.25
$AUC_{(0-24)}$ (μg•h/ml)	37.5±6.6	8.12±11.4	168±34.0	56.4±12.3	87.4±25.0
$AUC_{(0-\infty)}$ (μg•h/ml)	40.9±8.2	85.3±13.6	181±44.0	59.5±13.1	92.5±25.0
F_R (%)	-	92.3	-	64.4	-

10.2.3. <u>BRIDGING PHARMACOKINETIC STUDY</u>

Bridging pharmacokinetic studies were performed in order to compare the plasma pharmacokinetic profiles of the T1249 bulk drug substances used in the nonclinical trials described above to the formulated T1249 drug product which would be administered to an actual subject or patient, *e.g.*, to treat HIV infection. The study was designed as a parallel group, one-way, cross-over comparison of three dose levels of T1249 bulk drug substance and three dose levels of formulated drug product. Plasma pharmacokinetics were assessed after single-dose administration and after steady state was achieved.

Administration of T1249 by subcutaneous injection resulted in measurable levels of peptide in all dose groups. The plasma concentration-time curves were roughly parallel within all dose groups following the initial dose (Days 1 and 15) and at steady state (Days 4 and 18) for both T1249 bulk drug substance and formulated T1249 drug product. Furthermore $AUC_{(0-12hr)}$ values varied in direct proportion to

the dose level for both drug formulations. Calculated $AUC_{(0-12hr)}$ values for the drug product ranged from 43% to 80% of the $AUC_{(0-12hr)}$ values calculated for drug substance following single dose administration, and from 36% to 71% at steady state.

T1249 bulk drug substance and drug product demonstrated similar pharmacokinetic profiles in cynomolgus monkeys following bolus subcutaneous administration at the dose levels and dose volume tested. A direct comparison of the shapes of the plasma concentration-time curves in the present study and the shapes of curves from a previous study in cynomolgus monkeys suggests that there is a depot effect when T1249 is administered by subcutaneous injection. This is suggested by the increases in time at which maximal plasma concentration (t_{max}) is achieved and $t_{1/2}$.

These results indicate that the formulation of bulk drug substance used in the pharmacology program yields comparable AUC values and other kinetic parameters to those observed following the administration of the formulated drug product. These observations indicate that clinical administration of T1249 will result in total patient exposure to T1249.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A hybrid polypeptide comprising an enhancer peptide sequence linked to a core polypeptide.

2. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence comprises: WXXWXXXI, WXXWXXX, WXXWXX, WXXWX, WXXW, WXXXWXWX, XXXWXWX, XXWXWX, XWXWX, WXWX, WXXXWXW, WXXXW, IXXXWXXW, XXXWXXW, XXWXXW, XWXXW, XWXXXW, XWXWXXX, XWXWXX, XWXWX, XWXW, WXWXXXW or XWXXXW.

3. The hybrid polypeptide of Claim 1 wherein the enhancer peptide sequence comprises WQEWEQKI or WASLWEWF.

4. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.

5. The hybrid polypeptide of Claim 4, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

6. The hybrid polypeptide of Claim 1, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

7. The hybrid polypeptide of Claim 1 wherein the core polypeptide is a therapeutic reagent.

8. The hybrid polypeptide of Claim 1 wherein the core polypeptide is a bioactive peptide, a growth factor, cytokine, differentiation factor, interleukin, interferon, colony stimulating factor, hormone or angiogenic factor amino acid sequence.

9. The hybrid polypeptide of Claim 1, wherein the core polypeptide comprises the following amino acid sequence: YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS;

LEANISQSLEQAQIQQEKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL; DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK; TALLEQAQIQQEKNEYELQKLDK; TALLEQAQIQQEKNEYELQKLDE; TALLEQAQIQQEKNEYELQKLIE; TALLEQAQIQQEKIEYELQKLDK; TALLEQAQIQQEKIEYELQKLDE; TALLEQAQIQQEKIEYELQKLIE; TALLEQAQIQQEKIEYELQKLE; TALLEQAQIQQEKIEYELQKLAK; TALLEQAQIQQEKIEYELQKLAE; TALLEQAQIQQEKAEYELQKLE; TALLEQAQIQQEKNEYELQKLE; TALLEQAQIQQEKGEYELQKLE; TALLEQAQIQQEKAEYELQKLAK; TALLEQAQIQQEKNEYELQKLAK; TALLEQAQIQQEKGEYELQKLAK; TALLEQAQIQQEKAEYELQKLAE; TALLEQAQIQQEKNEYELQKLAE; TALLEQAQIQQEKGEYELQKLAE; DEFDASISQVNEKINQSLAFIRKSDELL; DEYDASISQVNEKINQALAYIREADEL; DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL; DEFDESISQVNEKIEESLAFIRKSDEL; or QHWSYGLRPG.

10. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence is linked to the amino-terminal end of the core polypeptide.

11. The hybrid polypeptide of Claim 10, further comprising an enhancer peptide sequence linked to the carboxy-terminal end of the core polypeptide.

12. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence is linked to the carboxy-terminal end of the core polypeptide.

13. The hybrid polypeptide of Claim 9, wherein the enhancer peptide sequence comprises WQEWEQKI or WASLWEWF.

14. The hybrid polypeptide of Claim 9, wherein the hybrid polypeptide comprises the amino acid sequence: WQEWEQKITALLEQAQIQQEKNEYELQKLDKWASLWEWF, WQEWEQKITALLEQAQIQQEKIEYELQKLIEWEWF or VYPSDEYDASISQVNEEINQALAYIRKADELLENV.

15. The hybrid polypeptide of Claim 14, further comprising an amino terminal acetyl group and a carboxy terminal amido group.

16. A core polypeptide comprising:
YTSLIHSLIEESQNQQEKNEQELLELDK; LEENITALLEEAQIQQEKNMYELQKLNS; LEANISQSLEQAQIQQEKNMYELQKLNS; NNYTSLIHSLIEESQNQQEKNEQELLEL; DFLEENITALLEEAQIQQEKNMYELQKL; RYLEANISQSLEQAQIQQEKNMYELQKL; RYLEANITALLEQAQIQQEKNEYELQKL; NNYTSLIHSLIEESQNQQEKNEQELLELDK;
TALLEQAQIQQEKNEYELQKLDK;
TALLEQAQIQQEKNEYELQKLDE;
TALLEQAQIQQEKNEYELQKLIE;
TALLEQAQIQQEKIEYELQKLDK;
TALLEQAQIQQEKIEYELQKLDE;
TALLEQAQIQQEKIEYELQKLIE;
TALLEQAQIQQEKIEYELQKLE;
TALLEQAQIQQEKIEYELQKLAK;
TALLEQAQIQQEKIEYELQKLAE;
TALLEQAQIQQEKAEYELQKLE;
TALLEQAQIQQEKNEYELQKLE;
TALLEQAQIQQEKGEYELQKLE;
TALLEQAQIQQEKAEYELQKLAK;
TALLEQAQIQQEKNEYELQKLAK;
TALLEQAQIQQEKGEYELQKLAK;

TALLEQAQIQQEKAEYELQKLAE;
TALLEQAQIQQEKNEYELQKLAE;
TALLEQAQIQQEKGEYELQKLAE;
DEFDASISQVNEKINQSLAFIRKSDELL;
DEYDASISQVNEKINQALAYIREADEL;
DEYDASISQVNEEINQALAYIRKADEL; DEFDESISQVNEKIEESLAFIRKSDELL;
DEFDESISQVNEKIEESLAFIRKSDEL; or
QHWSYGLRPG.

17. The core polypeptide of Claim 16, further comprising an amino terminal acetyl group and a carboxy terminal amido group.

18. A method for enhancing the pharmacokinetic properties of a core polypeptide comprising linking a consensus enhancer peptide sequence to a core polypeptide to form a hybrid polypeptide, such that, when introduced into a living system, the hybrid polypeptide exhibits enhanced pharmacokinetic properties relative those exhibited by the core polypeptide.

19. The method of Claim 18 wherein the core polypeptide is a therapeutic reagent.

20. The method of Claim 18 wherein the core polypeptide is a bioactive peptide, growth factor, cytokine, differentiation factor, interleukin, interferon, colony stimulating factor, hormone or angiogenic factor.

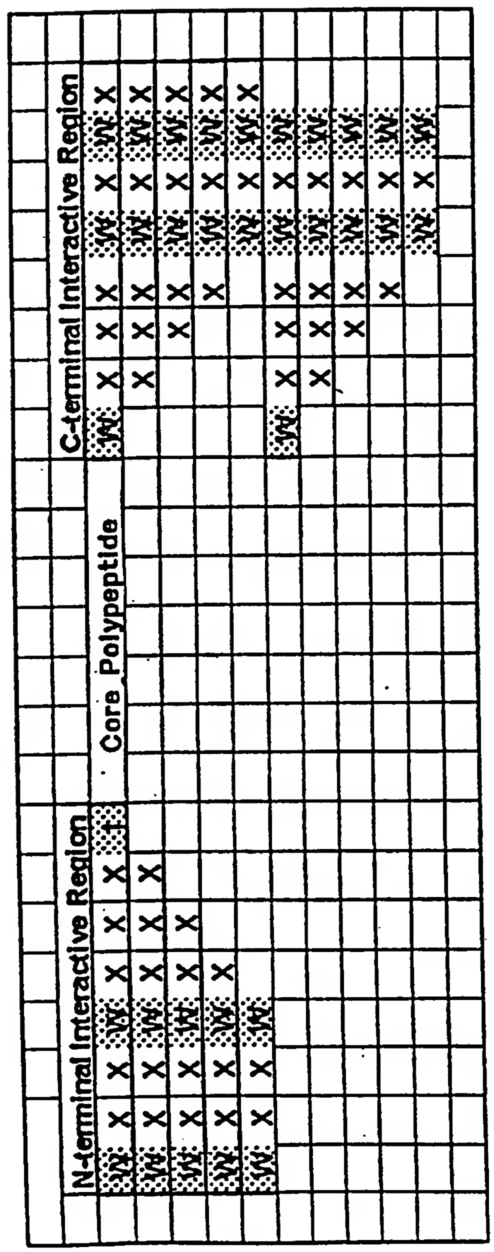

N-terminal Interactive Region
Core Polypeptide
C-terminal Interactive Region

FIGURE 1

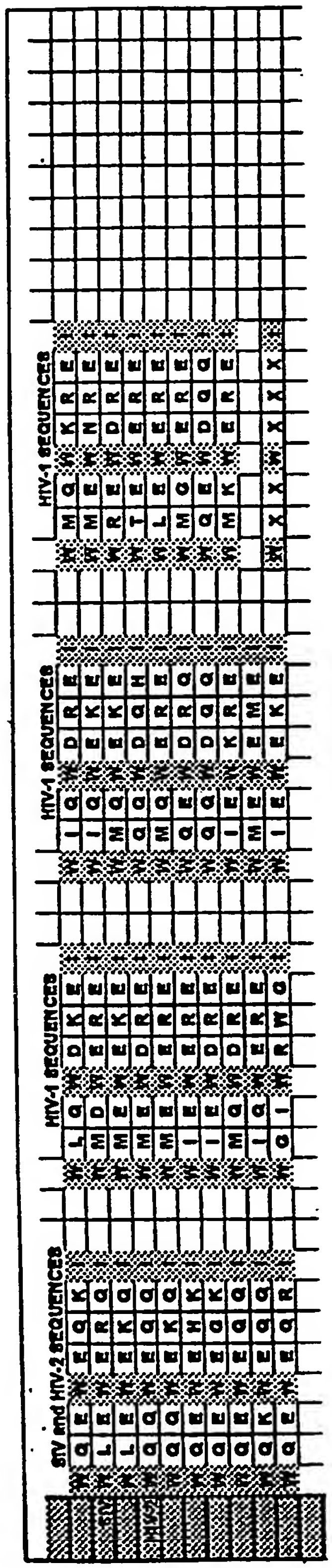


FIGURE 2A

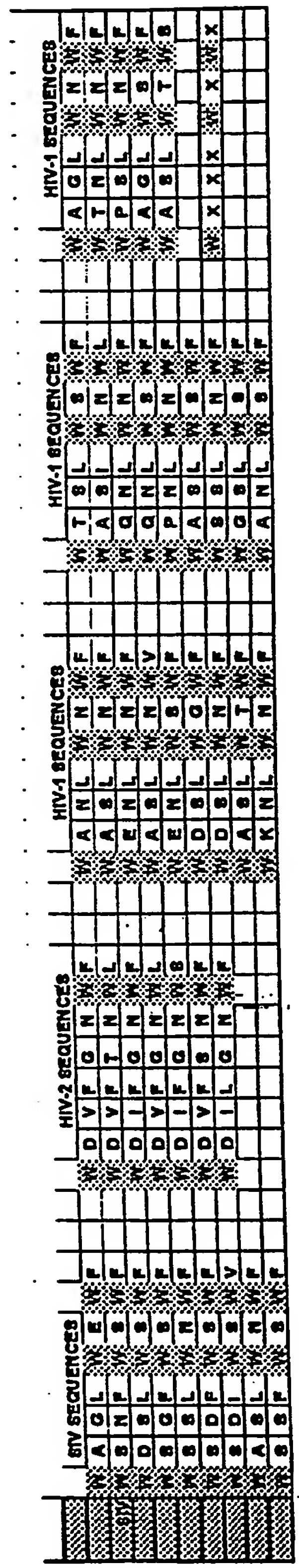


FIGURE 2B

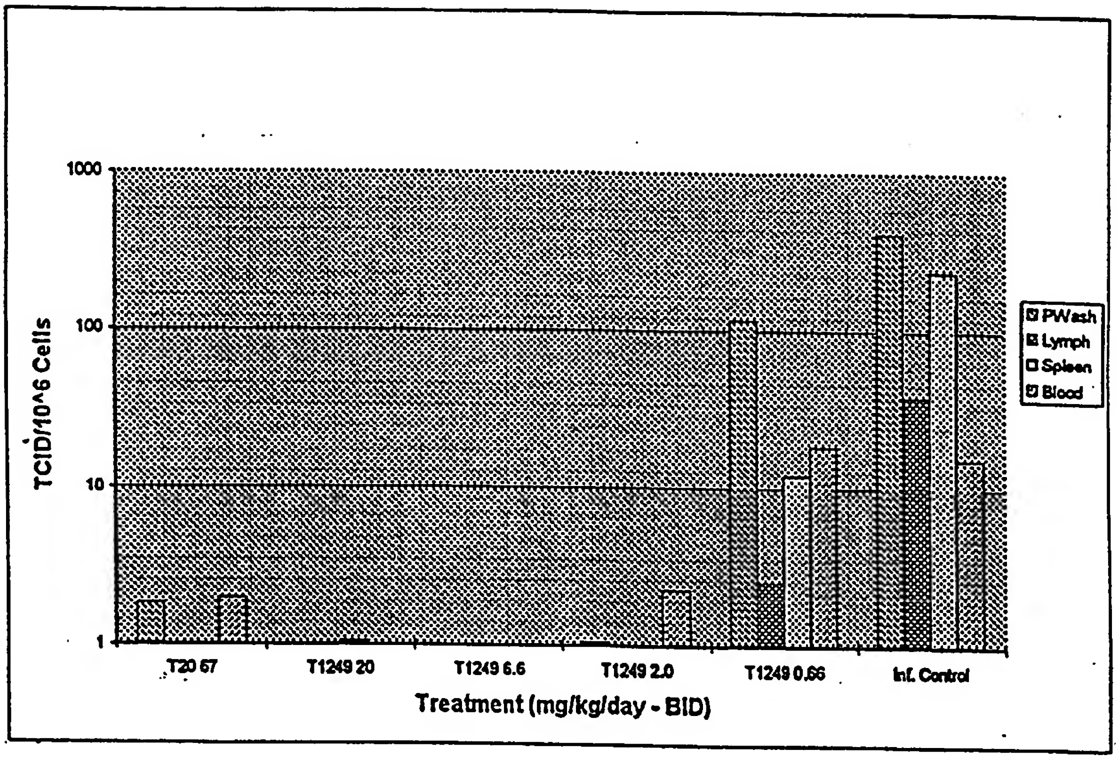

1000
100
10
1
TCID/10^6 Cells
PWash
Lymph
Spleen
Blood
T20 67
T1249 20
T1249 6.6
T1249 2.0
T1249 0.66
Inf. Control
Treatment (mg/kg/day - BID)

FIGURE 3

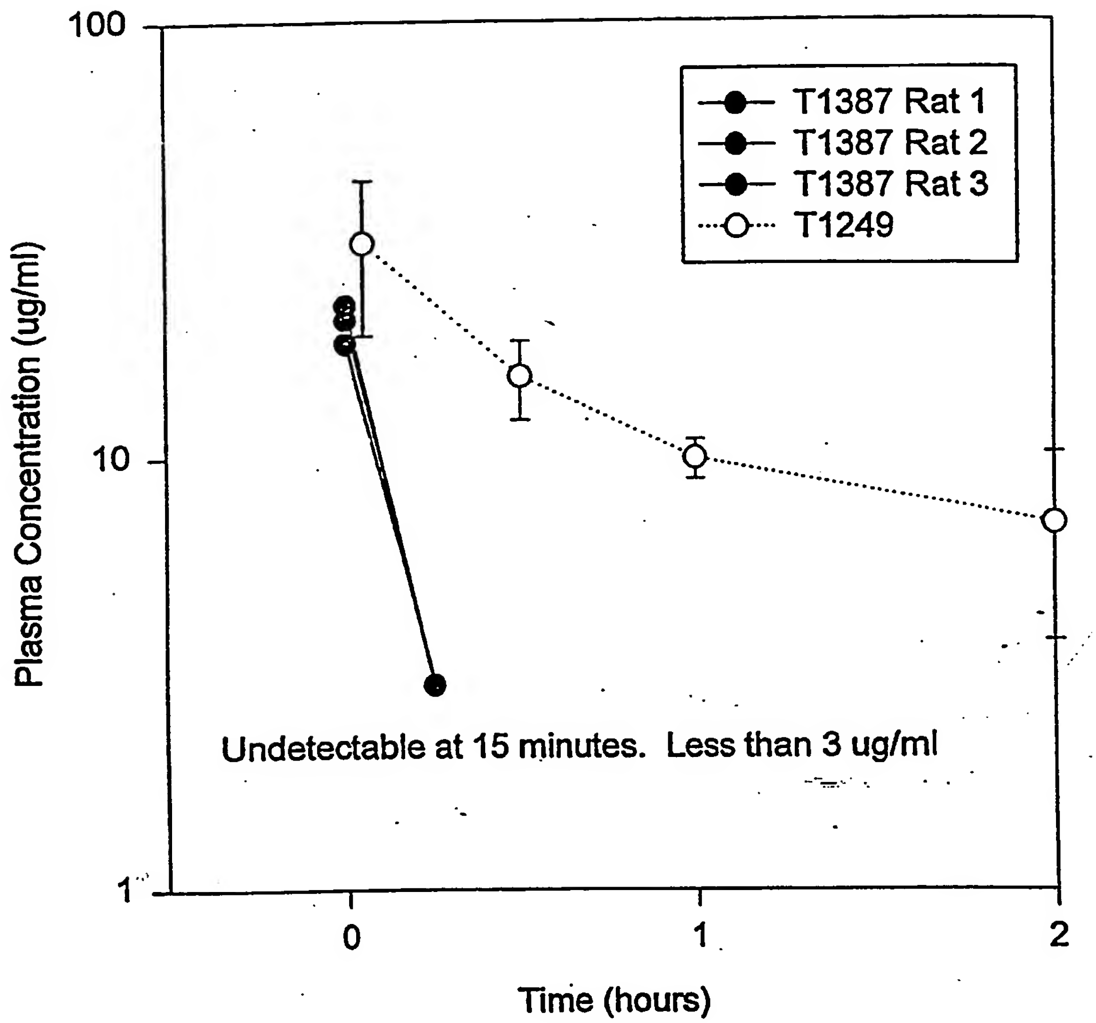

100
10
1
Plasma Concentration (ug/ml)
T1387 Rat 1
T1387 Rat 2
T1387 Rat 3
T1249
Undetectable at 15 minutes. Less than 3 ug/ml
0
1
2
Time (hours)

FIGURE 4A

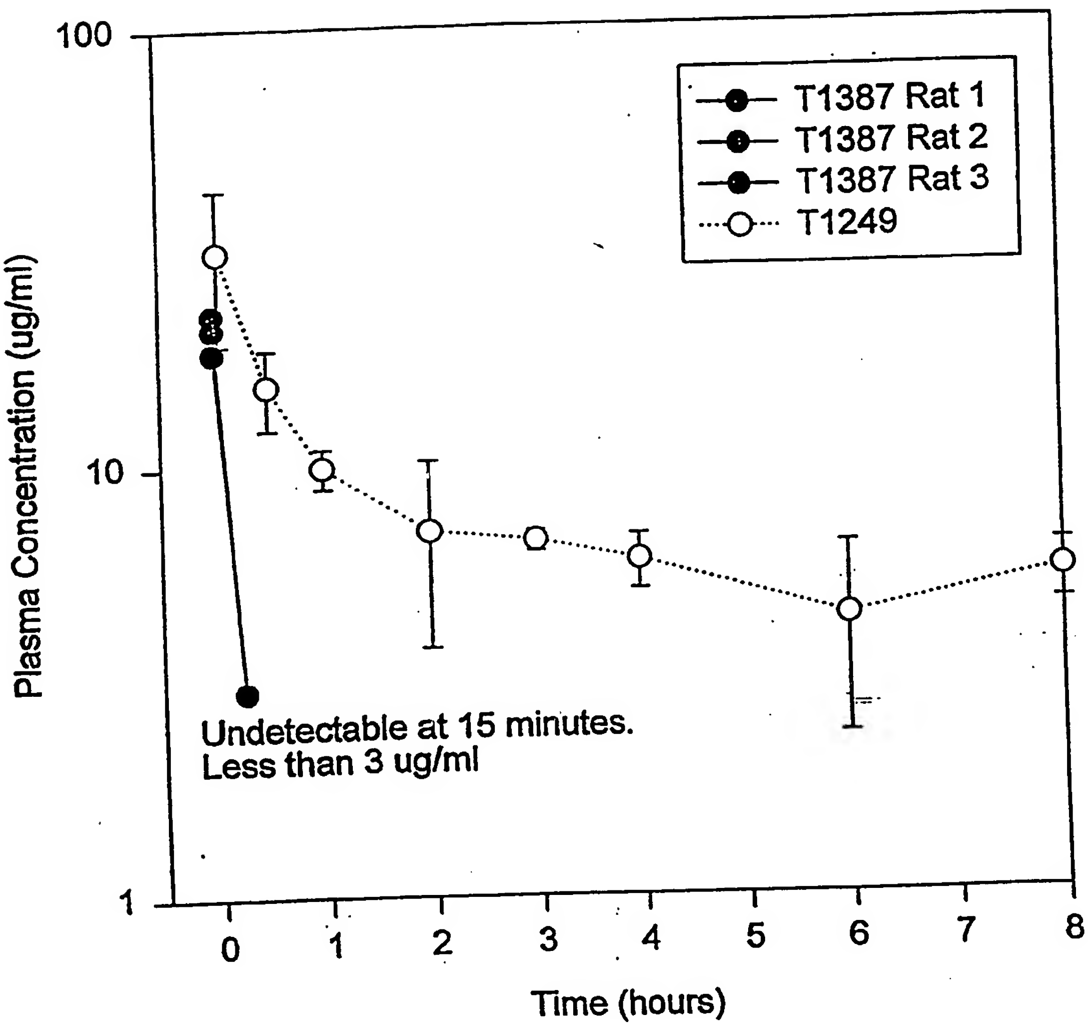
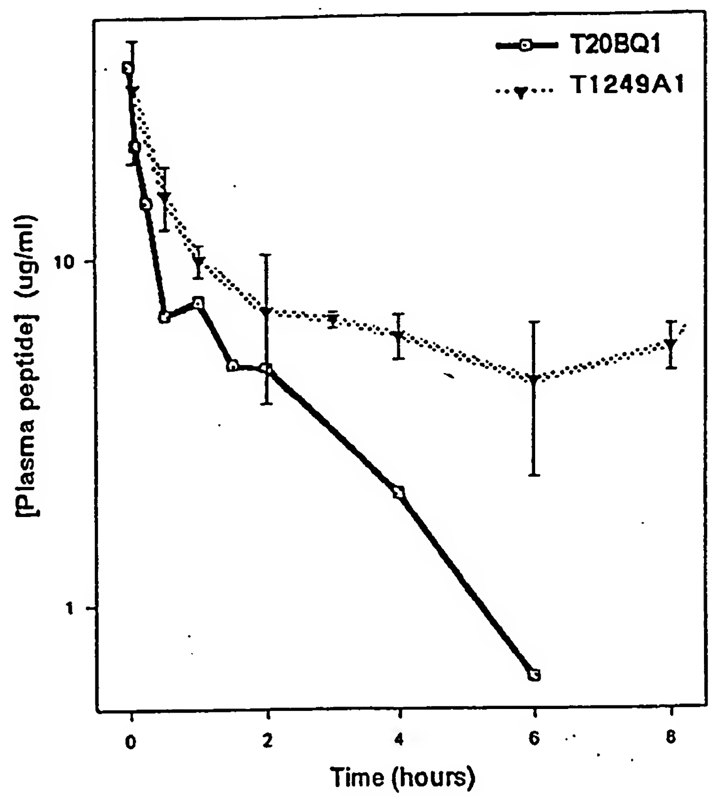

100
10
1
Plasma Concentration (ug/ml)
0
1
2
3
4
5
6
7
8
Time (hours)
T1387 Rat 1
T1387 Rat 2
T1387 Rat 3
T1249
Undetectable at 15 minutes.
Less than 3 ug/ml

FIGURE 4B



Pharmacokinetic Parameters	T20BQ1	T1249A1
Dose (mg/kg IV)	2.5	2.5
Detection method	Fluorescence HPLC	Fluorescence HPLC
$T_{1/2\beta}$ (h)	1.6	4.71
Cl_{β} (ml/h)	27.94	9.62
$AUC_{[0-8]}$ (ug·h/ml)	26.12	71.43

FIGURE 5

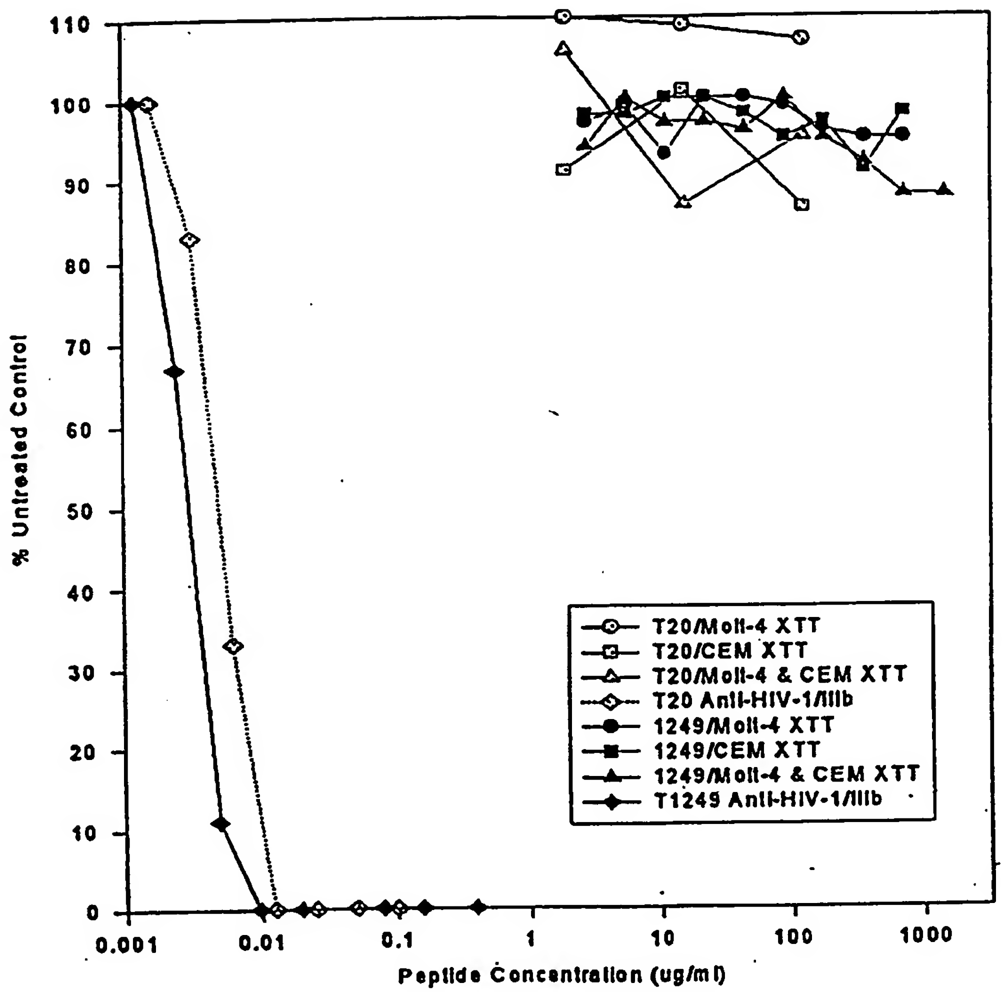
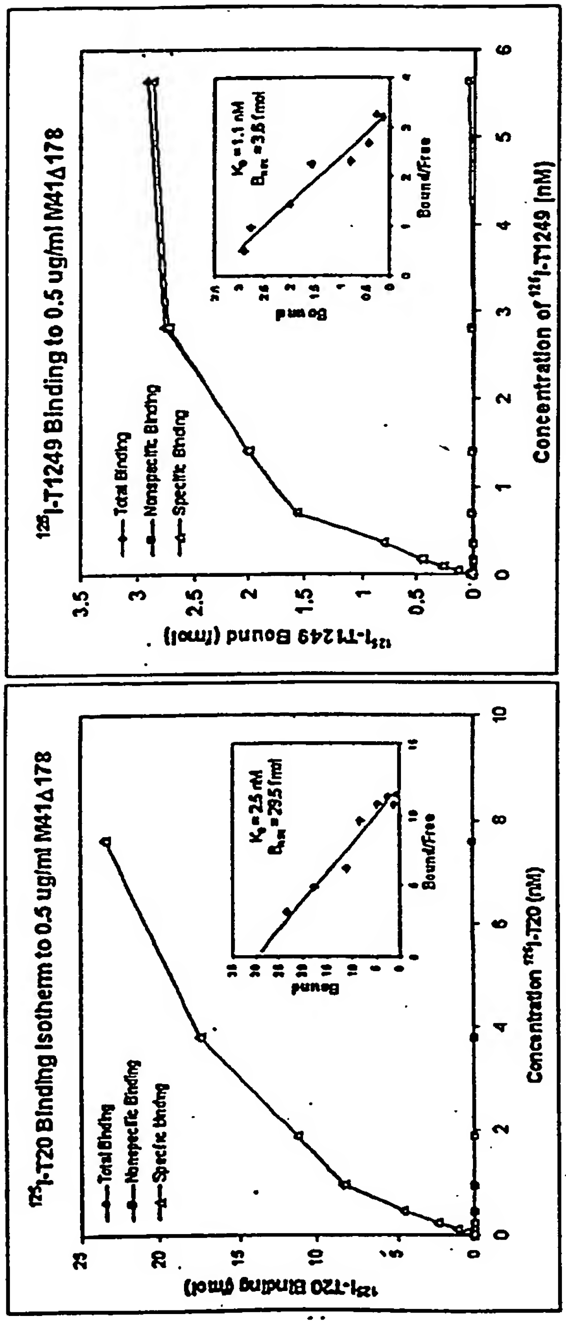

110
100
90
80
70
60
50
40
30
20
10
0
% Untreated Control
0.001
0.01
0.1
1
10
100
1000
Peptide Concentration (ug/ml)
T20/Molt-4 XTT
T20/CEM XTT
T20/Molt-4 & CEM XTT
T20 Anti-HIV-1/IIIb
1249/Molt-4 XTT
1249/CEM XTT
1249/Molt-4 & CEM XTT
T1249 Anti-HIV-1/IIIb

FIGURE 6



125I-T1249 Binding to 0.5 ug/ml M41Δ178
Total Binding
Nonspecific Binding
Specific Binding
125I-T1249 Bound (fmol)
Concentration of 125I-T1249 (nM)
Kd = 1.1 nM
Bmax = 3.6 fmol
Bound
Bound/Free
125I-T20 Binding Isotherm to 0.5 ug/ml M41Δ178
Total Binding
Nonspecific Binding
Specific Binding
125I-T20 Binding (fmol)
Concentration 125I-T20 (nM)
Kd = 2.5 nM
Bmax = 29.5 fmol
Bound
Bound/Free

FIGURE 7

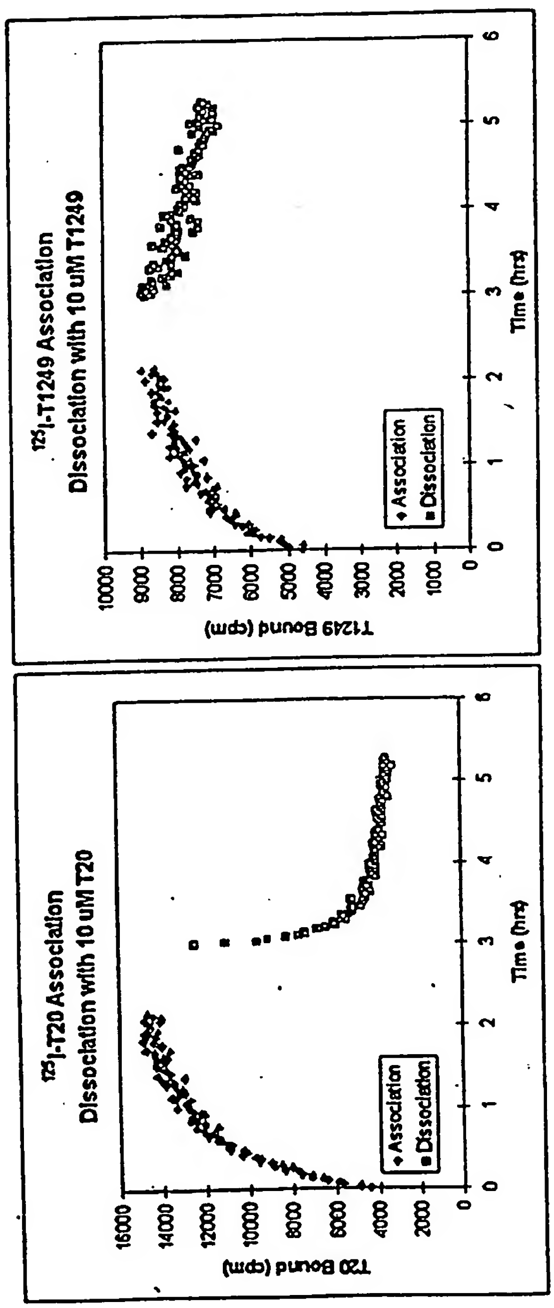

125I-T1249 Association
Dissociation with 10 uM T1249
T1249 Bound (cpm)
Time (hrs)
Association
Dissociation
125I-T20 Association
Dissociation with 10 uM T20
T20 Bound (cpm)
Time (hrs)
Association
Dissociation

FIGURE 8

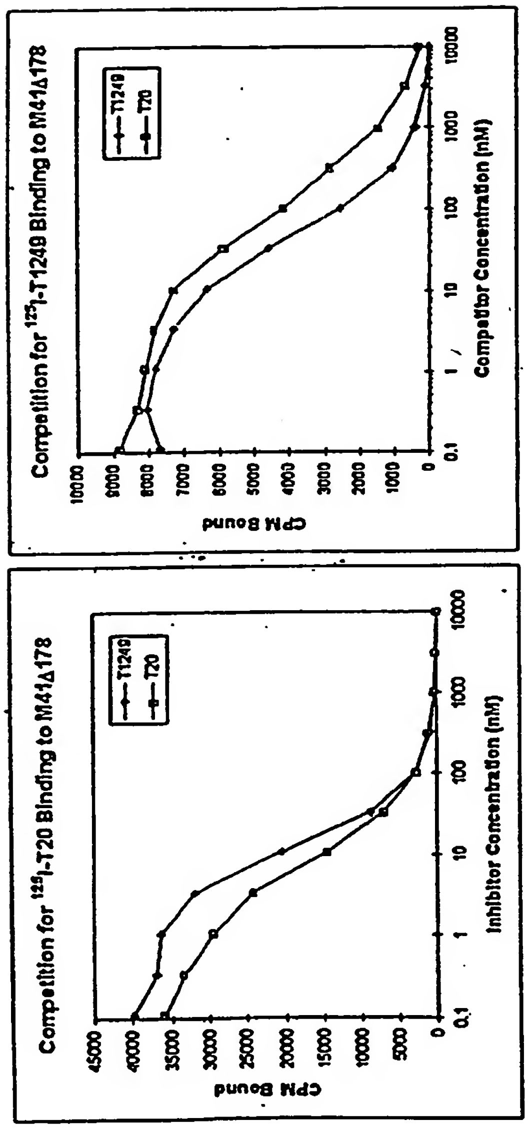

Competition for 125I-T1249 Binding to M41Δ178
CPM Bound
Competitor Concentration (nM)
T1249
T20
Competition for 125I-T20 Binding to M41Δ178
CPM Bound
Inhibitor Concentration (nM)
T1249
T20

FIGURE 9

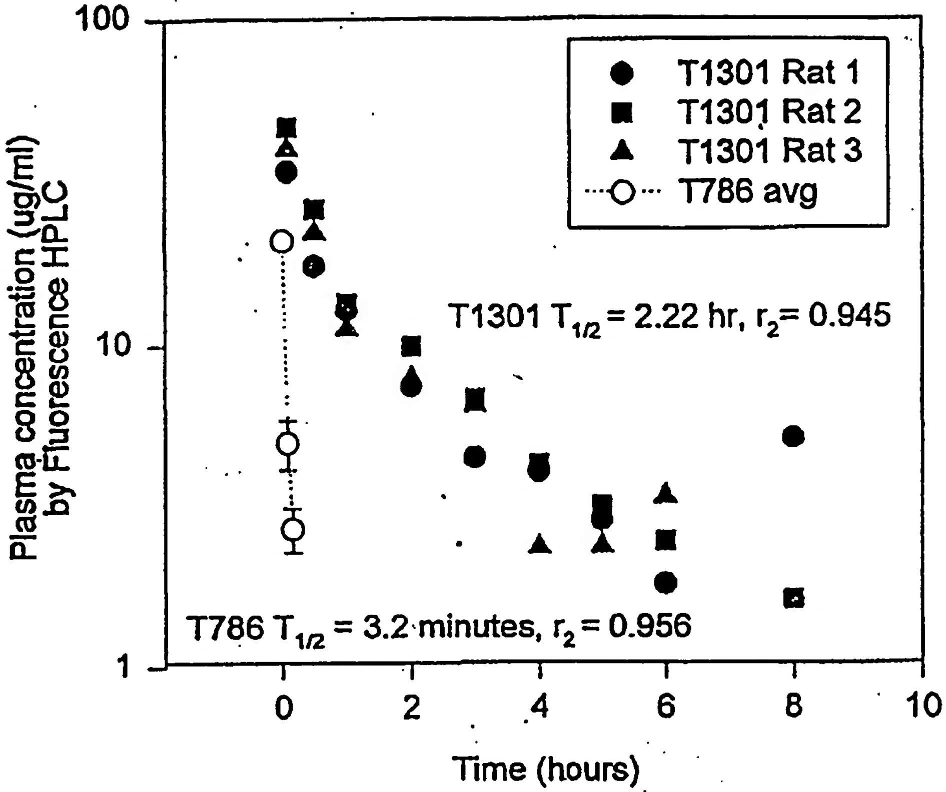

100
10
1
Plasma concentration (ug/ml) by Fluorescence HPLC
T1301 Rat 1
T1301 Rat 2
T1301 Rat 3
T786 avg
T1301 T1/2 = 2.22 hr, r2 = 0.945
T786 T1/2 = 3.2 minutes, r2 = 0.956
0
2
4
6
8
10
Time (hours)

FIGURE 10A

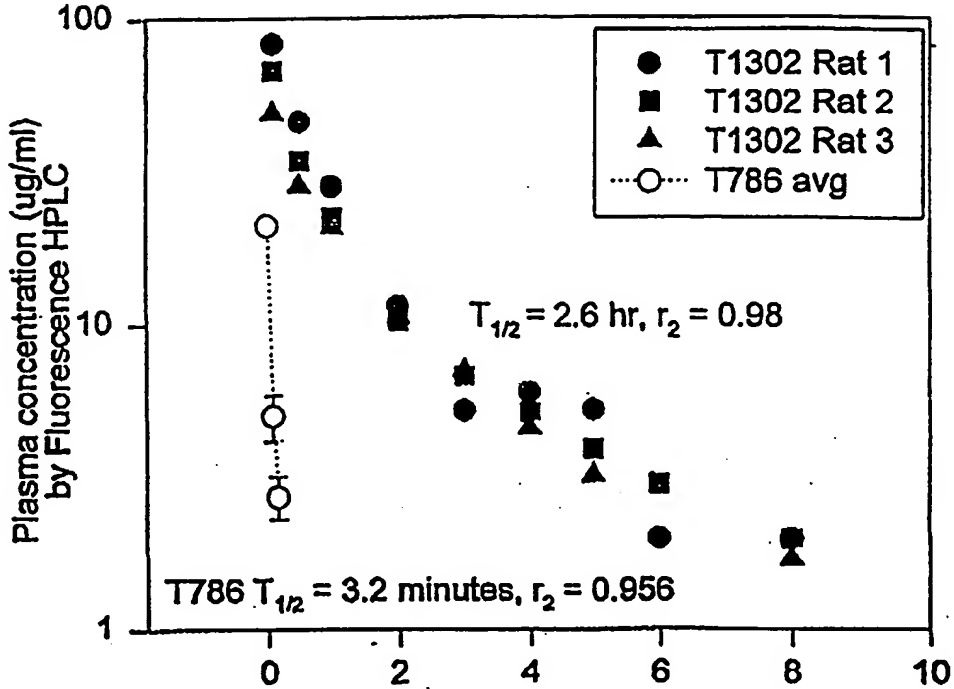

100
10
1
Plasma concentration (ug/ml) by Fluorescence HPLC
T1302 Rat 1
T1302 Rat 2
T1302 Rat 3
T786 avg
$T_{1/2}$ = 2.6 hr, r_2 = 0.98
T786 $T_{1/2}$ = 3.2 minutes, r_2 = 0.956
0
2
4
6
8
10

FIGURE 10B

Virus= RSV

Concentration-ug/ml		2 50.000	3 25.000	4 12.500	5 6.250	6 3.125	7 1.563	8 0.781	9 0.391	10 0.195	11 0.098	12 0.100	Infected Control
	T1302A1	3	4	7	13	24	29	31	38	39	41	41	43
	T786P3	0	1	2	5	12	20	31.	34	34	38	38	43
	T1293	4	7	8	9	17	20	31	34	43	43	43	43

% Inhibition		50.000	25.000	12.500	6.250	3.125	1.563	0.781	0.391	0.195	0.098	0.049	IC50 ug/ml
	T1302A1	0.93	0.91	0.84	0.70	0.44	0.33	0.28	0.12	0.09	0.05	0.05	2.68129
	T786P3	1.00	0.98	0.95	0.88	0.72	0.53	0.28	0.21	0.21	0.16	0.16	1.03566
	T1293	0.91	0.84	0.81	0.79	0.60	0.53	0.28	0.21	0.00	0.00	0.00	2.24562

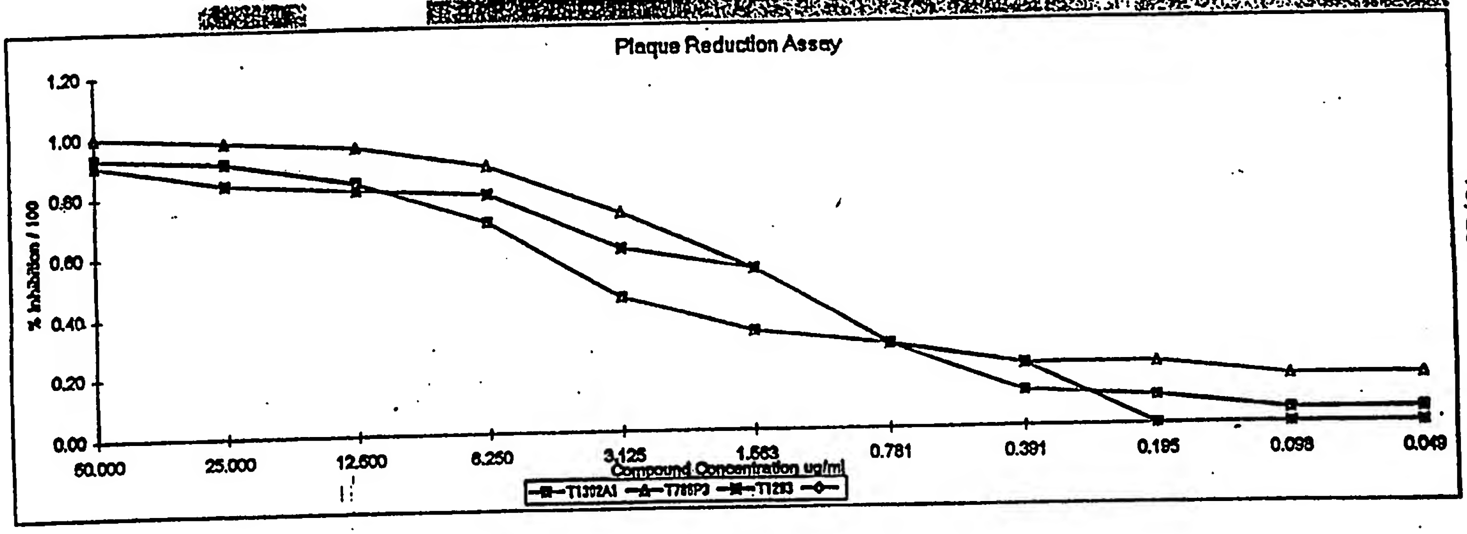


FIGURE 11A

Virus= RSV

Concentration-ug/ml		2 50.000	3 25.000	4 12.500	5 6.250	6 3.125	7 1.563	8 0.781	9 0.391	10 0.195	11 0.098	12 0.100	Infected Control
	T1301A1	0	2	4	12	17	28	40	40	42	42	42	42
	T1302A1	2	4	6	10	16	21	33	42	42	42	42	42
	T1303A1	5	8	8	11	28	28	31	32	42	42	42	42

% Inhibition	[redacted]	50.000	25.000	12.500	6.250	3.125	1.563	0.781	0.391	0.195	0.098	0.049	IC50 ug/ml
	T1301A1	1.00	0.95	0.90	0.71	0.60	0.38	0.05	0.05	0.00	0.00	0.00	2.83039
	T1302A1	0.95	0.90	0.86	0.76	0.62	0.50	0.21	0.00	0.00	0.00	0.00	2.62159
	T1303A1	0.88	0.81	0.81	0.74	0.38	0.33	0.26	0.24	0.00	0.00	0.00	3.22987

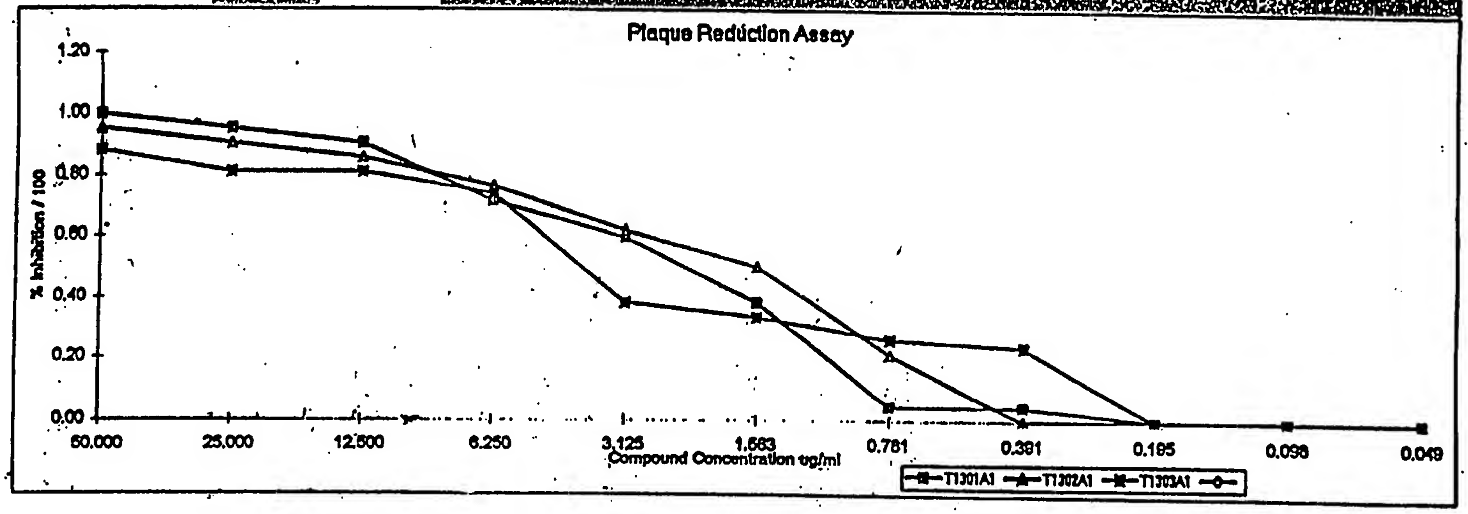


FIGURE 11 B

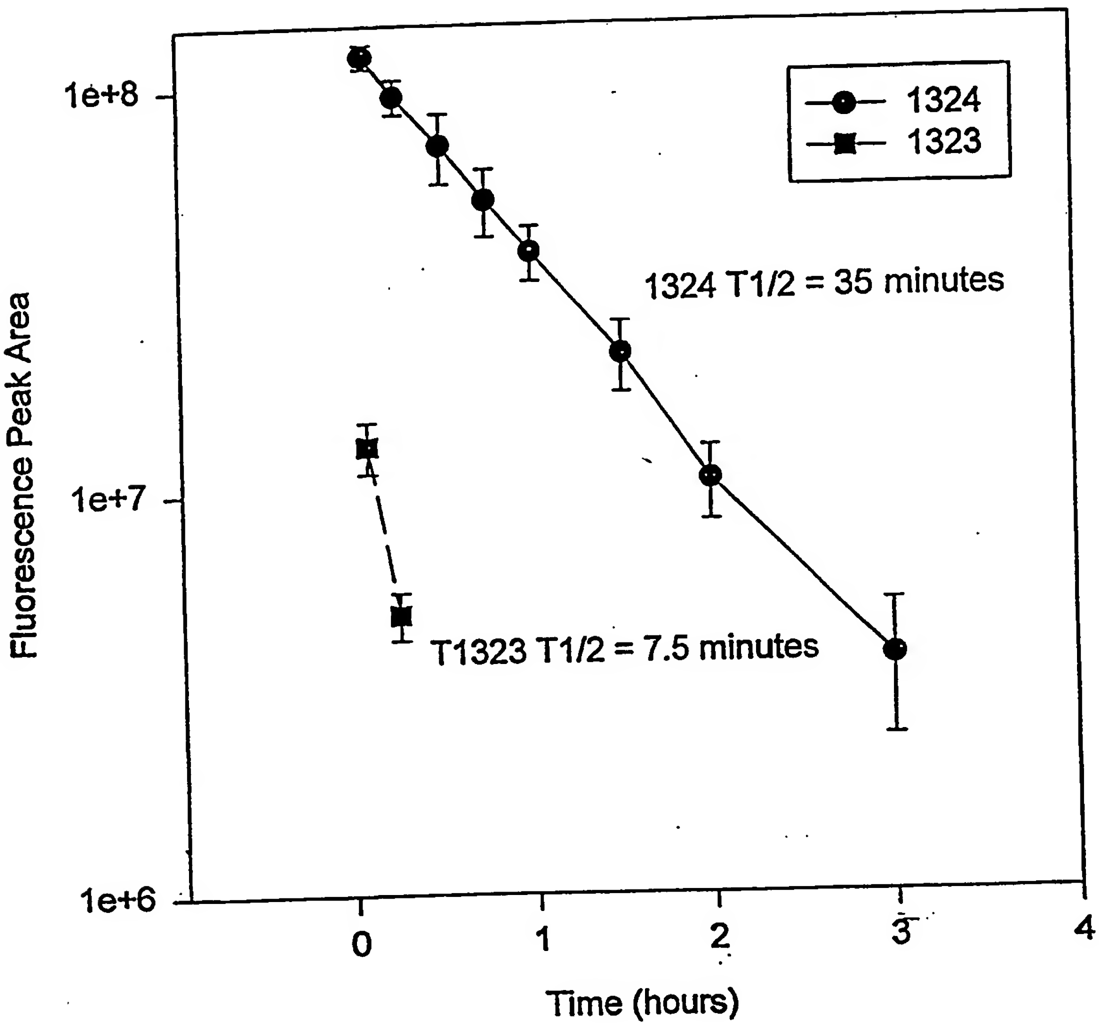
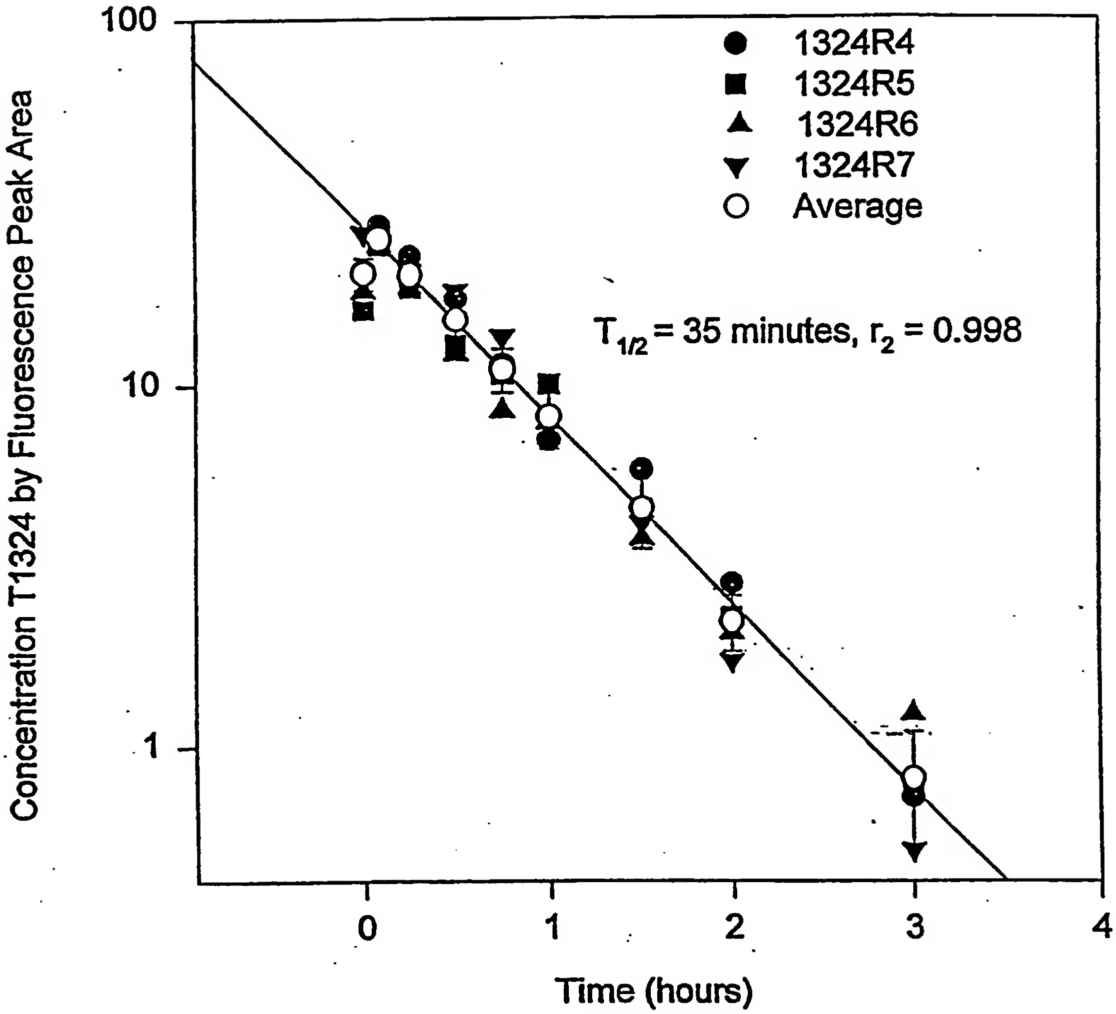

Fluorescence Peak Area
1e+8
1e+7
1e+6
1324
1323
1324 T1/2 = 35 minutes
T1323 T1/2 = 7.5 minutes
0
1
2
3
4
Time (hours)

FIGURE 12A



100
10
1
Concentration T1324 by Fluorescence Peak Area
1324R4
1324R5
1324R6
1324R7
Average
$T_{1/2}$ = 35 minutes, r_2 = 0.998
0
1
2
3
4
Time (hours)

FIGURE 12B

Peptide	HIV-1 Fusion EC-50 ng/ml	RSV Fusion EC-50 ng/ml
HIV-1 T20	3	>50000
HIV-1 T379	3	
SIV T402	3	
HIV-2 T198	50	
HIV-1 T640	7	
SIV T191	10	
HIV-2 T198	7	
HYBRID T1062	9	
HIV-1 T626	7	
HIV-1 T166	5	
HIV-1 T167	8	
HYBRID T1387	>10000	
HYBRID T1388	>10000	
HYBRID T1226	4	
HYBRID T1227	7	
HYBRID T1268	6	
HYBRID T1307		
HYBRID T1309	3	
HYBRID T1311	63	
HYBRID T1314	30	
HYBRID T1312	13	
HYBRID T1313	3	
HYBRID T1276	6	
HYBRID T1275	7	
HYBRID T1277	3	
HYBRID T1279	6	
HYBRID T1273	3	
HYBRID T1290	7	
HYBRID T1247	1	
HYBRID T1249	1	
HYBRID T1253	2	
HYBRID T1330	25	2946
HYBRID T1331	30	11136
HYBRID T1332	16	
HYBRID T1333	23	
HYBRID T1334	35	
HYBRID T1347	8	3613
HYBRID T1350	8	4616
HYBRID T1348	7	8273
HYBRID T1351	8	20617
HYBRID T1349	86	15336
HYBRID T1352	173	14318
HYBRID T1329	13	367
HYBRID T1293	11	3061
HYBRID T1337	4	21916
HYBRID T1336	234	879
HYBRID T1294	22	7774
HYBRID T1389	153	>50000
HYBRID T1391	3	24387
HYBRID T1392	4	3090
HYBRID T1393	23	2393
HYBRID T1394	21	21022
HYBRID T1396	66	>50000

FIGURE 13

Peptide	Sequence	C-term	IV t1/2	Biological Activity: Peptide	RSV Fusion EC-50 ng/ml	RSV Fusion EC-50 ng/ml
RSV T67	[illegible]	-NH2	<5m	RSV T67	800	
RSV T729	Ac- V Y P S [illegible] R N V	-NH2	<5m	RSV T729	1700	3000
T67 Active Core Sequence						
HYBRID T1178	Ac- Y T S L I H S L G G [illegible] G G W A S L W N W F	-NH2		HYBRID T1178	1000	
HYBRID T1185	Ac- Y T S L I H S L G G [illegible]	-NH2		HYBRID T1185	200	
HYBRID T1187	Ac- Y T S L G G [illegible] G G W N W F	-NH2		HYBRID T1187		
HYBRID T1186	Ac- Y T S L G G [illegible]	-NH2		HYBRID T1186	750	
HYBRID T1187	Ac- [illegible] G G W A S L W N W F	-NH2		HYBRID T1187	3000	
HYBRID T1188	Ac- [illegible] G G W N W F	-NH2		HYBRID T1188		
HYBRID T1179	Ac- W N W F [illegible] W N W F	-NH2		HYBRID T1179	2900	
T729 Active Core Sequence						
T1473	[illegible]	-NH2		T1473		
T1474	Ac- [illegible]	-NH2		T1474		
HYBRID T1296	Ac- [illegible] W E W F	-NH2		HYBRID T1296	1800	
HYBRID T1293	Ac- W Q E W D R E I [illegible] W E W F	-NH2		HYBRID T1293		
HYBRID T1298	Ac- W Q E W D R E I [illegible] W E W F	-NH2		HYBRID T1298		
HYBRID T1299	Ac- W Q E W E R E I [illegible] W E W F	-NH2		HYBRID T1299		
HYBRID T1297	Ac- W Q E W E R I [illegible] W E W F	-NH2		HYBRID T1297	1900	
HYBRID T1290	Ac- W Q E W E I [illegible] W E W F	-NH2		HYBRID T1290	3200	
HYBRID T1291	Ac- W Q E W E I [illegible] W E W F	-NH2		HYBRID T1291	2000	
HYBRID T1292	Ac- W Q E W [illegible] W E W F	-NH2		HYBRID T1292	2100	
HYBRID T1301	Ac- W Q E W [illegible] W A W F	-NH2	2.2h	HYBRID T1301	1700	
HYBRID T1302	Ac- W Q A W [illegible] W A W F	-NH2	2.8h	HYBRID T1302	2000	
HYBRID T1303	Ac- W Q A W [illegible] W E W F	-NH2		HYBRID T1303	1200	
LH-RH T1323	Ac- [illegible]	-NH2	7m	LH-RH T1323	N/A	
LH-RH Core Sequence						
HYBRID T1326	Ac- W N W F [illegible] W N W F	-NH2		HYBRID T1326	N/A	
HYBRID T1327	Ac- F N F F [illegible] F N F F	-NH2		HYBRID T1327	N/A	
HYBRID T1328	Ac- Q A Q A [illegible] A Q A Q	-NH2		HYBRID T1328	N/A	
HYBRID T1324	Ac- W Q E W E Q K I [illegible] W A S L W E W F	-NH2	23m	HYBRID T1324	N/A	
HYBRID T1325	Ac- W Q E W E Q K I [illegible] W E W F	-NH2		HYBRID T1325	N/A	
HYBRID T1364	Ac- W Q E W [illegible] W E W F	-NH2		HYBRID T1364	N/A	
HYBRID T1375	Ac- W Q A W [illegible] W A W F	-NH2		HYBRID T1375	N/A	

FIGURE 13 cont'd.

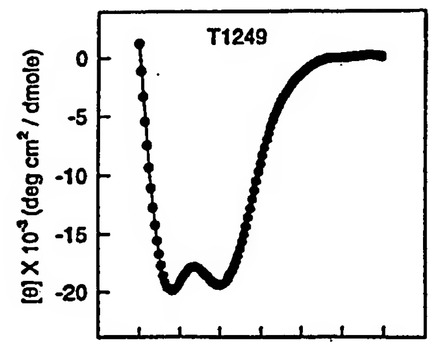


FIGURE 14A

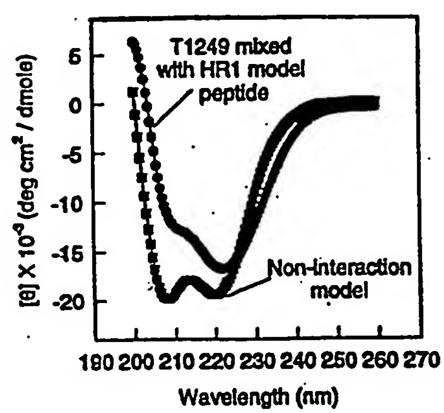


FIGURE 14B

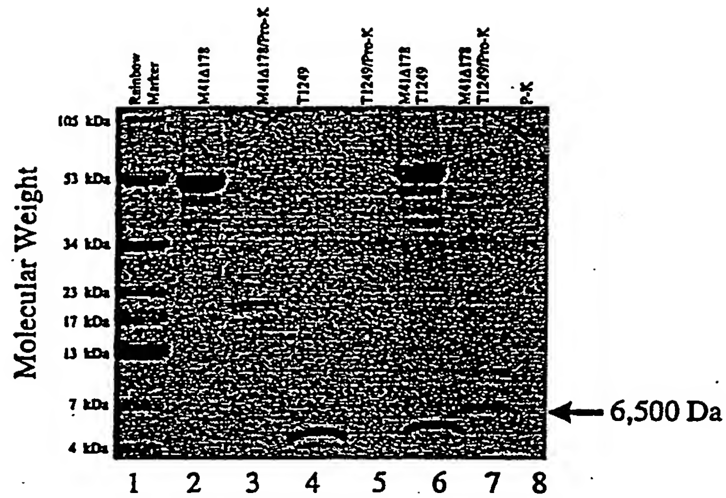

Rainbow Marker
M41Δ178
M41Δ178/Pro-K
T1249
T1249/Pro-K
M41Δ178 T1249
M41Δ178 T1249/Pro-K
P-K
Molecular Weight
105 kDa
53 kDa
34 kDa
23 kDa
17 kDa
13 kDa
7 kDa
4 kDa
6,500 Da
1
2
3
4
5
6
7
8

FIGURE 15

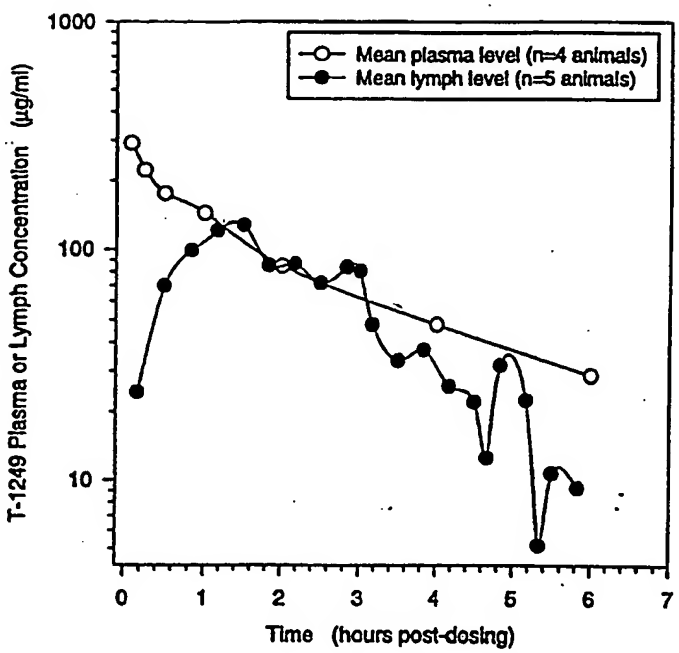

1000
100
10
T-1249 Plasma or Lymph Concentration (µg/ml)
Mean plasma level (n=4 animals)
Mean lymph level (n=5 animals)
0
1
2
3
4
5
6
7
Time (hours post-dosing)

FIGURE 16C

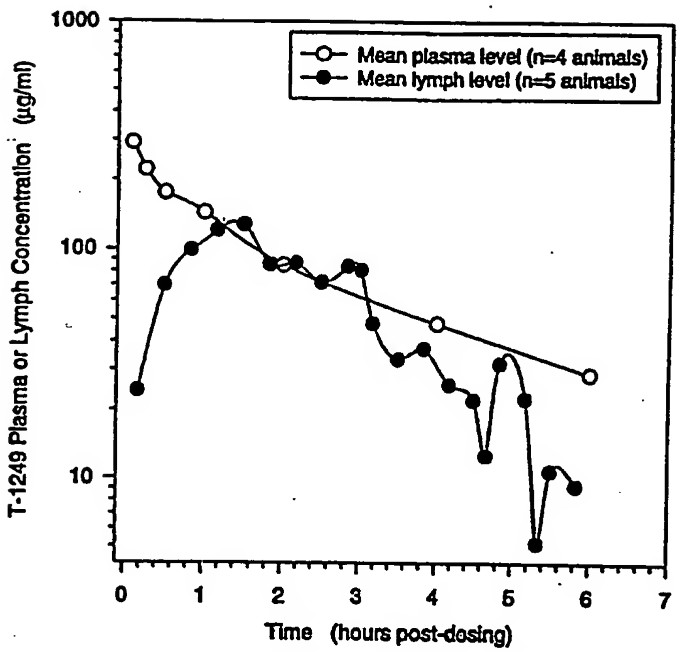

1000
100
10
T-1249 Plasma or Lymph Concentration (µg/ml)
Mean plasma level (n=4 animals)
Mean lymph level (n=5 animals)
0
1
2
3
4
5
6
7
Time (hours post-dosing)

FIGURE 16C

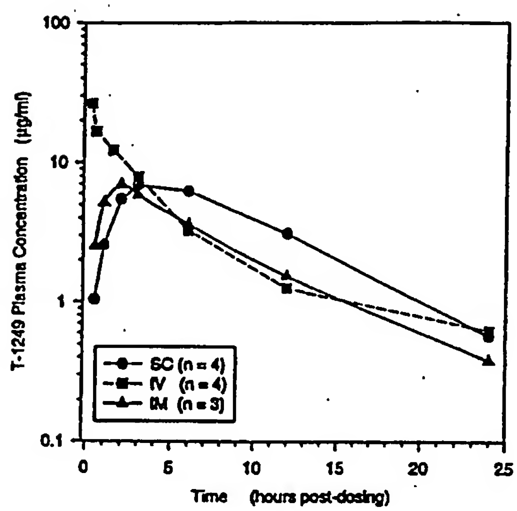


FIGURE 17A

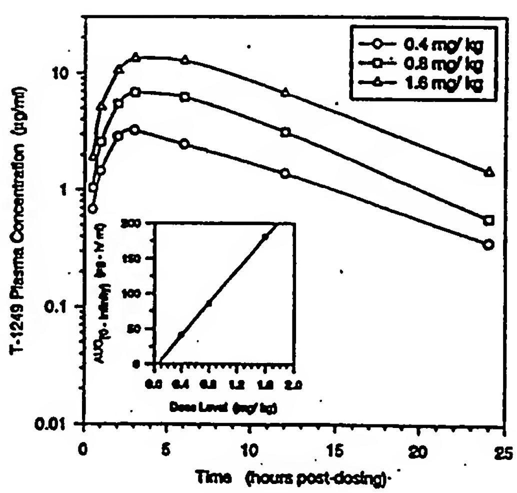


FIGURE 17B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11219

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/300, 313, 324, 326, 328, 350, 397, 398, 399; 514/2, 12, 13, 15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, GENESEQ, SWISSPROT, PIR, STN
search terms: hybrid, chimeric, sequences of claims 9 and 16

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,723,129 A (POTTER ET AL) 03 March 1998 (03/03/98), abstract, column 4, lines 36-43, SEQ ID NO:8, especially residues 953-962.	1, 4, 7-10, 16, 18-20
X,P	US 5,763,160 A (C. WANG) 09 June 1998 (09/06/98), column 9, line 60 - column 10, line 39, column 15, line 25 - column 16, line 41, column 18, line 65 - column 19, line 10, column 20, lines 53-64.	1, 6-8, 18-20
X,P	US 5,843,913 A (LI ET AL) 01 December 1998 (01/12/98), Figure 2, SEQ ID NO:2. especially residues 506-533.	16
X	EP 0 272 858 A2 (REPLIGEN CORPORATION) 29 June 1988 (29/06/88), page 9, line 54 - page 10, line 23, page 17, line 1, page 18, lines 11-15, Table 3.	1, 2, 4-12, 16, 18-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 AUGUST 1999	21 OCT 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer D. Lawrence for JEFFREY E. RUSSEL Telephone No. (703) 308-0196

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 306 912 A2 (ALBANY MEDICAL COLLEGE) 15 March 1989 (15/03/89).	1-20
X	EP 0 578 293 A1 (AKZO N.V.) 12 January 1994 (12/01/94), page 3, lines 35-58, page 4, lines 45-49.	1, 2, 4-12, 16, 18-20
X	WO 91/07664 A1 (CAMBRIDGE BIOSCIENCE CORPORATION) 30 May 1991 (30/05/91), page 4, lines 17-26, page 10, lines 9-17, Examples 3 and 4, Figures 4, 8, 12, 15, and 21.	1, 2, 4, 6-8, 18-20
A	WO 91/09872 A3 (UNIVAX BIOLOGICS, INC.) 11 July 1991 (11/07/91).	1-20
X	WO 93/14207 A1 (CONNAUGHT LABORATORIES LIMITED) 22 July 1993 (22/07/93), abstract, Figures 1 and 5.	1, 4, 7-10, 16, 18-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11219

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 38/02, 38/08, 38/10, 38/16, 38/18, 38/19, 38/22; C07K 7/06, 7/08, 14/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

530/300, 313, 324, 326, 328, 350, 397, 398, 399; 514/2, 12, 13, 15